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(54) Title: CROSS-REACTIVE MONOCLONAL AND POLYCLONAL ANTIBODIES WHICH RECOGNIZE SURFACE PROTEINS FROM COAGULASE-NEGATIVE STAPHYLOCOCCI AND STAPHYLOCOCCUS AUREUS

(57) Abstract: Polyclonal and monoclonal antibodies which are cross-reactive to both coagulase-positive staphylococcus bacteria, such as *S. hemolyticus*, are provided which can recognize surface proteins from both coagulase-positive and coagulase negative staph bacteria. The antibodies may be generated from surface proteins that have been isolated on the basis of characteristics that may be common between *S. aureus* and coagulase-negative staphylococci, and these recombinant surface proteins are used to generate the antibodies of the invention. There is also provided vaccines and methods which utilize these proteins and antibodies for the treatment or protection against a wide variety of staphylococcal infections.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/19220

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : G01 N 33/569; C12 N 5/06, 5/16; C07 K 16/00
US CL : 435/7.33, 326, 332, 530/388.2, 388.4

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/7.33, 326, 332, 530/388.2, 388.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q9L470, 100% identical to SEQ.ID.NO: 21, SEQ.ID.NO: 19.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99QY4, 99.8% identical to SEQ.ID.NO: 18.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99QZ2, 97.4% identical to SEQ.ID.NO: 16.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99XE9, 92 % identical to SEQ.ID.NO: 12.	1-16, 19 and 21

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 September 2003 (28.09.2003)	19 FEB 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Padmavathi v Baskar Telephone No. (703)308-0196

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INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99UX5, 97.8 % identical to SEQ.ID.NO: 10.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99UX4, 98.8 % identical to SEQ.ID.NO: 8.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q931P4· 96.7 % identical to SEQ.ID.NO: 6 and Accession number Q99TD3, 96.6 % identical to SEQ.ID.NO: 6	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99QY4, 98.6 % identical to SEQ.ID.NO: 4.	1-16, 19 and 21
Y	Database SPTREMBL, Swiss Institute for Bioinformatics, SIB (Geneva, Switzerland), The European Bioinformatics Institute ,EBI (Cambridge, UK) Accession number Q99TB0, 91.6 % identical to SEQ.ID.NO: 2.	1-16, 19 and 21
Y	OHLSEN. K. et al Effects of subinhibitory concentrations of antibiotics on alpha-toxin (hla) gene expression of methicillin-sensitive and methicillin-resistant Staphylococcus aureus isolates.Antimicrob Agents Chemother, November1998 , Vol 42, No.11, pages 2817-2823.	1-16, 19 and 21

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International application No.
PCT/US02/19220

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.: Please See Continuation Sheet

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions 1-58 which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups 1- 21 Claim(s) 1-14, 16, 19, 21 and 15, drawn to an isolated antibodies that bind to SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19, 21, nucleic acid sequence encoding amino acid sequences SEQ.ID.NOS: 1, 3, 5,7,9, 11, 13, 15, 20 and the nucleic sequences coding for the A domain of the Aap protein or degenerate.

Groups 22-33 Claims 20 and 22 drawn to fragment of the DsqA protein and a vaccine comprising a protein SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19 and 21

Groups 34-45 Claim 17drawn to a method for treating or preventing S.aureus infection using antibodies that bind to SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19 and 21.

Groups 46-57 Claim 18 drawn to a method inducing an immune response using protein SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19 and 21.

The inventions listed as Groups 1-58 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group 1, claim(s) 1-14, 16, 19, 21 and 15, claim(s) 1-14, 16, 19, 21 drawn to an isolated antibodies that bind to SEQ.ID.NOS: 2, diagnostic kit comprising antibody to SEQ.ID.NOS: 2, pharmaceutical compostion comprising said antibody and a method of diagnosing S.aureus infection using said antibody which is the first product and first product of use.

Pursuant to PCT Rule 13.2 the ISA/US considers that where multiple products, processes and methods are claimed, the main invention shall consists of the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories related thereto. Accordingly the main invention (Group 1) comprises the first product and a method of use.

Further pursuant to PCT Rule 13.2 the ISA/US considers that any feature which the subsequently recited products and methods share with the main invention does not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention. Therefore, the groups of inventions below do not constitute a special technical feature within the meaning of PCT Rule 13.2 and that each of such products and methods accordingly defines a separate invention.

Groups 2-21 drawn to different isolated antibodies that bind to SEQ.ID.NOS: 4, 6,8,10, 12, 14, 16, 17, 18, 19, 21, nucleic acid sequence encoding amino acid sequences SEQ.ID.NOS: 1, 3, 5,7,9, 11, 13, 15, 20 and the nucleic sequences coding for the A domain of the Aap protein or degenerate that are different to each other and lack the same or corresponding special technical features because each antibody bind to a protein having a specific amino acid sequence. They are structurally different to each other since each sequence has been identified with a specific sequence identification number that contains specific amino acids. In the instant case the different inventions represent structurally different antibodies that bind to different polypeptides. Therefore, where structural identity is required, such as for expression, the different sequences have different effects. Thus, each sequence is unique and lacks the same or corresponding special technical features.

Groups 22-33 drawn to fragment of the DsqA protein and a vaccine comprising a protein SEQ.ID.NOS: 2, 4, 6,8,10, 12, 14, 16, 17, 18, 19, and 21. These proteins are different to each other and lack the same or corresponding special technical features because each protein contains a specific amino acid sequence. They are structurally different to each other since each sequence has been identified with a specific sequence identification number that contains specific amino acids. In the instant case the different inventions represent structurally different proteins. Therefore, where structural identity is required, such as for expression, the different sequences have different effects. Thus, each sequence is unique and lacks the same or corresponding special technical features

INTERNATIONAL SEARCH REPORT

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Groups 34-45 and 46-57 are different methods utilizing different products of antibodies or proteins that are unique and lack the same or corresponding special technical features that result in a different outcome such as preventing an infection with antibody or inducing an immune response with specific protein. These methods are different to each other in utilizing different reagents such as different polypeptides and antibodies as discussed above and thus lack the same or special technical features as explained above.

Continuation of Box II Item 3:
1-16, 19 and 21 with respect to SEQ.ID.NOS: 2, 4, 6, 8, 10, 12,16, 18, 19 and 21

Continuation of B. FIELDS SEARCHED Item 3:
SEQ.ID.NOS: 2, 4, 6, 8, 10, 12, 14, 16, 19, 17, 18 and 21 searched on MEDLINE, STN, A -GENSEQ, N-GENSEQ,EST, DERWENT, SWISS-PROT, PIR, USPTOWEST, SWISSSPTREMBL, GENEMBEL, PUBLISHED APPLICATIONS AND ISSUED PATENTS

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: CROSS-REACTIVE MONOCLONAL AND POLYCLONAL ANTIBODIES WHICH RECOGNIZE SURFACE PROTEINS FROM COAGULASE-NEGATIVE STAPHYLOCOCCI AND STAPHYLOCOCCUS AUREUS

(57) Abstract: Polyclonal and monoclonal antibodies which are cross-reactive to both coagulase-positive staphylococcus bacteria, such as S. *hemolyticus*, are provided which can recognize surface proteins from both coagulase-positive and coagulase negative staph bacteria. The antibodies may be generated from surface proteins that have been isolated on the basis of characteristics that may be common between S. *aureus* and coagulase-negative staphylococci, and these recombinant surface proteins are used to generate the antibodies of the invention. There is also provided vaccines and methods which utilize these proteins and antibodies for the treatment or protection against a wide variety of staphylococcal infections.

CROSS-REACTIVE MONOCLONAL AND POLYCLONAL ANTIBODIES WHICH RECOGNIZE SURFACE PROTEINS FROM COAGULASE-NEGATIVE STAPHYLOCOCCI AND STAPHYLOCOCCUS AUREUS

Cross Reference to Related Applications

The present application claims the benefit of U.S. provisional application Ser. No. 60/298,098 filed June 15, 2001.

Field of the Invention

The present invention relates in general to surface proteins from *Staphylococcus aureus* and their active regions such as their A domains which have homologue proteins on coagulase-negative Staphylococci such as *S. epidermidis* and *S. hemolyticus* as well as antibodies which recognize said proteins, and in particular to isolated monoclonal and polyclonal antibodies which recognize specific proteins from *Staphylococcus aureus* and coagulase-negative Staphylococci and which are cross-reactive against *S. aureus* and coagulase-negative Staphylococci and can thus be utilized in vaccines and methods useful for preventing or treating a wide variety of infections caused by staphylococcal bacteria.

Background of the Invention

The successful colonization of the host is a process required for most microorganisms to cause infections in animals and humans. Microbial adhesion is the first crucial step in a series of events that can eventually lead to disease. Pathogenic microorganisms colonize the host by attaching to host tissues or serum conditioned implanted biomaterials, such as catheters, artificial joints, and vascular grafts, through specific adhesins present on the surface of the bacteria. MSCRAMM®s (**M**icrobial **S**urface **C**omponents **R**ecognizing **A**dhesive **M**atrix **M**olecules) are a family of cell surface adhesins that recognize and specifically bind to distinct components in the host's extracellular matrix. Once the bacteria have successfully adhered and colonized host tissues, their physiology is dramatically altered and damaging components such as toxins and proteolytic enzymes are secreted. Moreover, adherent bacteria often produce a biofilm and quickly become more resistant to the killing effect of most antibiotics.

S. aureus causes a spectrum of infections that range from cutaneous lesions such as wound infections, impetigo, and furuncles to life-threatening conditions that include pneumonia, septic arthritis, sepsis, endocarditis, and biomaterial related infections. *S. aureus* is known to express a repertoire of different MSCRAMMs that can act individually or in concert to facilitate microbial adhesion to specific host tissue components. In addition, another type of staphylococcus bacteria is identified as the coagulase-negative bacteria, including such species as *S. epidermidis* and *S. hemolyticus* which are also have been known to express MSCRAMMs, and which also are responsible for a wide range of bacterial infections and related diseases. In this regard, MSCRAMMs generally provide an excellent target for immunological attack by antibodies, both polyclonal and monoclonal antibodies.

However, because antibodies by nature are very specific and in the case of different types of Staphylococci, such as *S. aureus* on one hand (coagulase-positive) and *S. epidermidis* and *S. hemolyticus* on the other (coagulase-negative), it has still remained a significant problem to develop antibodies that exhibit cross-reactivity across the different types of bacteria. Such cross-reactive antibodies are particularly desirable because of their potential in immunizing human and animal patients and providing protection against infections caused by both types of Staphylococcal bacteria, namely coagulase-positive bacteria such as *S. aureus* and the coagulase-negative bacteria, such as *S. epidermidis* and *S. hemolyticus*. Such antibodies would thus be extremely useful in preventing or treating a wide variety of the infections caused by staphylococcal bacteria.

Summary of the Invention

Accordingly, it is an object of the present invention to provide monoclonal antibodies that recognize MSCRAMM®'s from both coagulase-positive bacteria such as *S. aureus* as well as MSCRAMM®'s from coagulase-negative bacteria, such as *S. epidermidis* and *S. hemolyticus*.

It is also an object of the present invention to identify and isolate MSCRAMM®'s from staphylococcal bacteria, as well as their active regions such as the A domain, which can be used to generate monoclonal and polyclonal antibodies that will be cross-reactive against both coagulase-positive and coagulase-negative staphylococci.

It is still further an object of the present invention to provide isolated antibodies that can recognize the A domain of surface proteins such as the DgsK protein from coagulase-negative staphylococci and at the same time recognize surface proteins such as the SasA protein from *Staphylococcus aureus*.

It is yet another object of the present invention to utilize the isolated proteins, A domains and antibodies of the invention to produce vaccines useful in the treatment or prevention of staphylococcal infections, and to provide methods wherein the vaccines and antibodies of the invention are used to prevent or treat a staphylococcal infection.

These and other objects are provided by virtue of the present invention which comprises the identification and isolation of surface proteins from one type of staphylococcal bacteria, such as coagulase-negative or coagulase-positive staph, which can give rise to cross-reactive antibodies which can recognize surface proteins of both types of staph and which can thus be utilized in vaccines and methods of treating or preventing a wide range of staphylococcal infections. The present invention also relates to the generation of both polyclonal and monoclonal antibodies from these surface proteins and their use in preventing or treating staphylococcal infections.

These embodiments and other alternatives and modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the present specification and/or the references cited herein, all of which are incorporated by reference.

Brief Description of the Drawing Figures

Figure 1 is a depiction of the primary structure of the in silico-predicted proteins in accordance with the present invention.

Figure 2 shows a Coomassie gel of the purified N-terminal recombinant His-tagged proteins expressing the orfs of the present invention.

Figures 3A-3C show Western blotting of *S. aureus* cell wall extracts showing probing with anti-KesK antibodies (Fig. 3A), anti-KnkA antibodies (Fig. 3B) and anti-DsqA antibodies (Fig. 3C), respectively.

Figures 4A-4B show Dot-blotting and Western immunoblotting of *Lactococcus lactis* expressing *S. aureus* MSCRAMM®s, namely KnkA (Fig. 4A) and KesK (Fig. 4B).

Figures 5A-5D representing the probing of recombinant LPXTG proteins in accordance with the present invention with convalescent sera examining *in vivo* expression, including RrKn and RrKN2 (Fig. 5A), Kesk1 and Kesk2A (Fig. 5B), KnkA (Fig. 5C) and DsqA2 (Fig. 5D).

Figure 6 shows a Western blot analysis demonstrating that rabbit polyclonal antibodies against *S. aureus* SasA cross-react with a protein released from the cell surface of *S. epidermidis* HB as well as the recombinant A-region from DsgK cloned from *S. epidermidis*.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with the present invention, there are provided specific surface proteins from coagulase-positive staphylococcal bacteria, such as *S. aureus* as well as from coagulase-negative staph such as *S. epidermidis* and *S. hemolyticus*, including active fragments thereof such as the A domains of these proteins or other epitotic regions which can generate antibodies that recognize the whole protein. In accordance with the invention, the identification and isolation of candidate peptide sequences and proteins was carried out based on some of the common features of the MSCRAMM®s ((Microbial Surface Components Recognizing Adhesive Matrix Molecules) which are in most cases are covalently anchored to the cell wall peptidoglycan. These surface proteins had the following common features which

were utilized in identifying and isolated the sequences of the present invention, namely: (i) an N-terminal signal peptide (approximately 40 residues in length) required for Sec-dependent secretion, (ii) a wall spanning domain either rich in proline and glycine residues or composed of serine and aspartate dipeptide repeats, (iii) an LPXTG motif required for covalent anchoring of the protein to the pentaglycine crossbridge in peptidoglycan, (iv) a hydrophobic membrane-spanning domain followed by (v) several positively charged residues.

In accordance with the invention, by exploiting the whole genome of *S. aureus* in light of the properties as set forth above, at least eight novel open reading frames encoding proteins with secretion and anchorage motifs indicative of MSCRAMMs were identified (i.e. bearing an N-terminal signal peptide and a C-terminal LPXTG motif followed by a hydrophobic domain and a positively charged tail). Table 1 illustrates the list of proteins identified including their distribution among *S. aureus* genomes, their protein size and C-terminal cell wall sorting sequence.

Table 1.

Name	Distribution	Size	C-terminus
EkeS	ENCSJM	2189 aa	**LPNTG**SEEMDLPLKELALITGAALLA**RRRS KKEKES**
DsqA	ENCSJM	~1363-2283 aa	**LPDTG**DSIKQNGLLGGVMTLLVGLGLM**KR KKKKDENDQDDSQ**A
KesK	ENCSJM	~909 aa	**LPKTG**ETTSSQSWWGLYALLGMLALFIP**K FRKESK**
KrkN2	ENCSJM (Cowan)	~278 aa	**LPKTG**LTSVDNFISTVAFATLALLGSLSLLLF **KRKESK**
KrkN	ENCSJM	~661 aa	**LPQTG**EESNKDMTLPLMALIALSSIVAFVLP **RKRKN**
RkaS	ENCSJM	~801 aa	**LPKTG**TNQSSSPEAMFVLLAGIGLIATV**RR RK**AS
RrkN	NCSJM	1629 aa	**LPKTG**LESTQKGLIFSSIIGIAGLMLLA**RRRK N**
KnkA	NCSJM	629 aa	**LPKAG**ETIKEHWLPISVIVGAMGVLMIWLS **RRNKLKNK**A

Abbreviations: eMRSA-16; N, 8325; C, COL; S, MSSA; J, N315, M, Mu50.
Six out of eight are conserved in all of the six staphylococcal genomes currently sequenced and the remaining two are present in 5/6 of these genomes.

In accordance with the invention, amino acid and nucleic acid sequences coding for the above proteins were obtained, and these were as follows: Ekes MRSA – SEQ ID NO:1 (DNA sequence); EkeS_MRSA – SEQ ID NO:2 (Protein sequence); DsqA (8325) – SEQ ID NO:3 (DNA sequence); DsqA (8325) – SEQ ID NO:4 (Protein sequence); KesK1 (8325) – SEQ ID NO:5 (DNA sequence); KesK1 (8325) – SEQ ID NO:6 (Protein sequence); KrkN2 (8325) — SEQ ID NO:7 (DNA sequence); KrkN2 (8325) – SEQ ID NO:8 (Protein sequence); KrkN (8325) – SEQ ID NO:9 (DNA sequence); KrkN (8325) – SEQ ID NO:10 (Protein sequence); RkaS (COL) – SEQ ID NO:11 (DNA sequence); RkaS (COL) – SEQ ID NO:12 (Protein sequence); RrkN (8325) – SEQ ID NO:13 (DNA sequence); RrkN (8325) – SEQ ID NO:14 (Protein sequence); KnkA (8325) – SEQ ID NO:15 (DNA sequence); KnkA (8325) – SEQ ID NO:16 (Protein sequence).

In accordance with the present invention, isolated antibodies may be generated from the above proteins or their active regions such as the A domain so as to be able to recognize said proteins and/or said domains. These antibodies may be either monoclonal or polyclonal. If polyclonal antibodies are desired, these may be generated in any of a number of conventional ways well known in the art. In a typical process, the desired surface protein or active region thereof may be injected into a suitable host animal, e.g., a mouse or rabbit, and after a suitable time period, antibodies may be isolated and recovered from the host animal. With regard to monoclonal antibodies, in accordance with the present invention, these may be produced in any number of suitable ways including, e.g., the well known method of Kohler and Milstein, Nature 256:495-497 (1975), or other suitable ways known in the field, such as those methods disclosed in U.S. Pat. Nos. 6,331,415; 5,981,216; 5,807,715; and 4,816,567; Eur. Pat. App. 519,596; and PCT publication WO 00/71585, all of these patent publications incorporated herein by reference. These methods include their preparation as chimeric, humanized, or human monoclonal antibodies in ways that would be well known in this field. Still further, monoclonal antibodies may be prepared from a single chain, such as the light or heavy chains, and in addition may be prepared from active fragments of an

antibody which retain the binding characteristics (e.g., specificity and/or affinity) of the whole antibody. By active fragments is meant an antibody fragment which has the same binding specificity as a complete antibody which binds to the particular surface protein or its homologue from the different type of staph bacteria (i.e., coagulase negative or coagulase-positive), and the term "antibody" as used herein is meant to include said fragments. Additionally, antisera prepared using monoclonal or polyclonal antibodies in accordance with the invention are also contemplated and may be prepared in a number of suitable ways as would be recognized by one skilled in the art.

As indicated above, antibodies to the isolated surface proteins and/or their active regions in accordance with the invention may be prepared in a number of suitable ways that would be well known in the art, such as the well-established Kohler and Milstein method described above which can be utilized to generate monoclonal antibodies. For example, in preliminary steps utilized in such a process, mice may be injected intraperitoneally once a week for a prolonged period with a purified recombinant MSCRAMM® in accordance with the invention or an active portion thereof, followed by a test of blood obtained from the immunized mice to determine reactivity to the purified protein. Following identification of mice reactive to the proteins, lymphocytes isolated from mouse spleens are fused to mouse myeloma cells to produce hybridomas positive for the antibodies against the surface proteins of the invention which are then isolated and cultured, following by purification and isotyping.

In order to generate monoclonal antibodies in accordance with the invention, it is preferred that these be generated using recombinantly prepared MSCRAMM®'s in accordance with the invention, and these recombinants may be generated and isolated using a number of standard methods well known in the art. For example, one such method employs the use of *E. coli* expression vector pQE-30 as an expression vector for cloning and expressing recombinant proteins and peptides. In one preferred method, using PCR, the A domain of the surface protein identified as DgsK or SasA was amplified from the sequences described above and subcloned

into the *E. coli* expression vector PQE-30 (Qiagen), which allows for the expression of a recombinant fusion protein containing six histidine residues. This vector was subsequently transformed into *E. coli* strain ATCC 55151, grown in a 15-liter fermentor to an optical density (OD_{600}) of 0.7 and induced with 0.2 mM isopropyl-1-beta-D galactoside (IPTG) for 4 hours. The cells were harvested using an AG Technologies hollow-fiber assembly (pore size 0.45 µm) and the cell paste frozen at –80° C. Cells were lysed in 1X PBS (10 mL buffer/1 g of cell paste) using 2 passes through the French Press @ 1100psi. Lysed cells were spun down at 17,000rpm for 30 minutes to remove cell debris. Supernatant was passed over a 5-mL HiTrap Chelating (Pharmacia) column charged with 0.1M $NiCl_2$. After loading, the column was washed with 5 column volumes of 10mM Tris, pH 8.0, 100mM NaCl (Buffer A). Protein was eluted using a 0-100% gradient of 10mM Tris, pH 8.0, 100mM NaCl, 200 mM imidazole (Buffer B) over 30 column volumes. SdrGN1N2N3 or SdrGN2N3 eluted at ~13% Buffer B (~26mM imidazole). Absorbance at 280nm was monitored. Fractions containing SdrGN1N2N3 or SdrGN2N3 were dialyzed in 1x PBS.

Next, each protein was then put through an endotoxin removal protocol. Buffers used during this protocol were made endotoxin free by passing over a 5-mL Mono-Q sepharose (Pharmacia) column. Protein was divided evenly between 4x 15mL tubes. The volume of each tube was brought to 9mL with Buffer A. 1mL of 10% Triton X-114 was added to each tube and incubated with rotation for 1 hour at 4°C. Tubes were placed in a 37°C water bath to separate phases. Tubes were spun down at 2,000rpm for 10 minutes and the upper aqueous phase from each tube was collected and the detergent extraction repeated. Aqueous phases from the 2nd extraction were combined and passed over a 5-mL IDA chelating (Sigma) column, charged with 0.1M $NiCl_2$ to remove remaining detergent. The column was washed with 9 column volumes of Buffer A before the protein was eluted with 3 column volumes of Buffer B. The eluant was passed over a 5-mL Detoxigel (Sigma) column and the flow-through collected and reapplied to the column. The flow-through from the second pass was collected and dialyzed in 1x PBS. The

purified product was analyzed for concentration, purity and endotoxin level before administration into the mice.

In the preferred process, monoclonal antibodies in accordance with the present invention may be prepared from the recombinant proteins identified above in the following manner. In this process, *E. coli* expressed and purified recombinant SasA and DsgK proteins were used to generate a panel of murine monoclonal antibodies while the mouse sera was used as a source of polyclonal antibodies. Briefly, a group of Balb/C or SJL mice received a series of subcutaneous immunizations of 1-10 mg of protein in solution or mixed with adjuvant as described below in Table 2.

Table 2. Immunization Schemes

RIMMS Injection	Day	Amount (µg)	Route	Adjuvant
#1	0	5	Subcutaneous	FCA/RIBI
#2	2	1	Subcutaneous	FCA/RIBI
#3	4	1	Subcutaneous	FCA/RIBI
#4	7	1	Subcutaneous	FCA/RIBI
#5	9	1	Subcutaneous	FCA/RIBI

Conventional Injection	Day	Amount (µg)	Route	Adjuvant
Primary	0	5	Subcutaneous	FCA
Boost #1	14	1	Intraperitoneal	RIBI
Boost #2	28	1	Intraperitoneal	RIBI
Boost #3	42	1	Intraperitoneal	RIBI

At the time of sacrifice (RIMMS) or seven days after a boost (conventional) serum was collected and titered in ELISA assays against MSCRAMM® proteins or on whole cells (S. *epidermidis* and *S. aureus*). Three days after the final boost, the spleens or lymph nodes were removed, teased into a single cell suspension and the lymphocytes harvested. Lymphocytes were then fused to a P3X63Ag8.653 myeloma cell line (ATCC #CRL-1580). Cell fusion, subsequent plating and feeding were performed according to the Production of Monoclonal Antibodies protocol from Current Protocols in Immunology (Chapter 2, Unit 2.), incorporated herein by reference.

Any clones that were generated from the fusion were then screened for specific anti-SasA antibody production using a standard ELISA assay. Positive clones were expanded and tested further for activity in a whole bacterial cell binding assay by flow cytometry and SasA binding by Biacore analysis. Throughout the Biacore analysis, the flow rate remained constant at 10 ml/min. Prior to the SasA or DgsK injection, test antibody was adsorbed to the chip via RAM-Fc binding. At time 0, SasA or DgsK at a concentration of 30 mg/ml was injected over the chip for 3 min followed by 2 minutes of dissociation. This phase of the analysis measured the relative association and disassociation kinetics of the Mab/SasA or DgsK interaction.

Next, the antibodies prepared as set forth above were tested for binding to whole bacteria. In these tests, bacterial samples *S. aureus* Newman, *S. aureus* 67-0, *S. aureus* 397 (Sal6), *S. aureus* Wood, *S. aureus* 8325-4, methicillin resistant *S. aureus* MRSA 16, *S. epidermidis* ATCC 35984, *S. epidermidis* HB, *S. epidermidis* CN-899 and *S. haemolyticus* ATCC 43253 were collected, washed and incubated with Mab or PBS alone (control) at a concentration of 2 µg/ml after blocking with rabbit IgG (50 mg/ml). Following incubation with antibody, bacterial cells were incubated with Goat-$F_{(ab')2}$-Anti-Mouse-$F_{(ab')2}$-FITC which served as the detection antibody. After antibody labeling, bacterial cells were aspirated through the FACScaliber flow cytometer to analyze fluorescence emission (excitation: 488, emission: 570). For each bacterial strain, 10,000 events were collected and measured. These data indicate that antibodies against *S. aureus* SasA were able to recognize a homologous protein on the surface of coagulase-negative staphylococci. The data support Western blot analysis demonstrating that rabbit polyclonal antibodies against *S. aureus* SasA cross-react with a protein released from the cell surface of *S. epidermidis* HB as well as the recombinant A-region from DsgK cloned from *S. epidermidis* (see Figure 6 and Table 3 below).

Table 3. Polyclonal Sera Reactivity

	Newman	67-0	397 (SAL6)	Wood 46	8325-4	MRSA 16	ATCC 3598	HB	CN-899	ATCC 4325

							4			3
Normal Mouse Sera	-	-	-	-	-	-	-	-	-	-
Mouse anti-SasA	+	+	+/-	-	+	+	+	+	+	+

Although production of antibodies using recombinant forms of the surface proteins of the present invention is preferred, antibodies may be generated from natural isolated and purified versions of these proteins or their active regions such as the A domain, and monoclonal or polyclonal antibodies can be generated using these proteins or active regions in the same manner as described above to obtain such antibodies. Still other conventional ways are available to generate the antibodies of the present invention using recombinant or natural purified proteins or their active regions, as would be recognized by one skilled in the art.

As would be recognized by one skilled in the art, the antibodies of the present invention may also be formed into suitable pharmaceutical compositions for administration to a human or animal patient in order to treat or prevent an infection caused by staphylococcal bacteria. Pharmaceutical compositions containing the antibodies of the present invention, or effective fragments thereof, may be formulated in combination with any suitable pharmaceutical vehicle, excipient or carrier that would commonly be used in this art, including such as saline, dextrose, water, glycerol, ethanol, other therapeutic compounds, and combinations thereof. As one skilled in this art would recognize, the particular vehicle, excipient or carrier used will vary depending on the patient and the patient's condition, and a variety of modes of administration would be suitable for the compositions of the invention, as would be recognized by one of ordinary skill in this art. Suitable methods of administering any pharmaceutical composition disclosed in this application include,

but are not limited to, topical, oral, anal, vaginal, intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal and intradermal administration.

For topical administration, the composition is formulated in the form of an ointment, cream, gel, lotion, drops (such as eye drops and ear drops), or solution (such as mouthwash). Wound or surgical dressings, sutures and aerosols may be impregnated with the composition. The composition may contain conventional additives, such as preservatives, solvents to promote penetration, and emollients. Topical formulations may also contain conventional carriers such as cream or ointment bases, ethanol, or oleyl alcohol. Additional forms of antibody compositions, and other information concerning compositions, vaccines, methods and applications with regard to other MSCRAMM®s will generally also be applicable to the present invention involving the aforementioned MSCRAMM®s and their active regions and antibodies thereto, and these other MSCRAMM®s are disclosed, for example, in U.S. patents 5,175,096; 5,320,951; 5,416,021; 5,440,014; 5,571,514; 5,652,217; 5,707,702; 5,789,549; 5,840,846; 5,980,908; 6,086,895; 6,008,341; 6,177,084; 5,851,794 and 6,288,214; all of these patents incorporated herein by reference.

The antibody compositions of the present invention may also be administered with a suitable adjuvant in an amount effective to enhance the immunogenic response. For example, suitable adjuvants may include alum (aluminum phosphate or aluminum hydroxide), which is used widely in humans, and other adjuvants such as saponin and its purified component Quil A, Freund's complete adjuvant, RIBBI adjuvant, and other adjuvants used in research and veterinary applications. Still other chemically defined preparations such as muramyl dipeptide, monophosphoryl lipid A, phospholipid conjugates such as those described by Goodman-Snitkoff *et al. J. Immunol.* 147:410-415 (1991) and incorporated by reference herein, encapsulation of the conjugate within a proteoliposome as described by Miller *et al.*, *J. Exp. Med.* 176:1739-1744 (1992) and incorporated by reference herein, and encapsulation of the protein in lipid

vesicles such as Novasome™ lipid vesicles (Micro Vescular Systems, Inc., Nashua, NH) may also be useful.

In any event, the antibody compositions of the present invention which recognize the proteins or their active regions as set forth above will be useful in methods of preventing or treating staphylococcal infection, and in inhibiting binding of staphylococcal bacteria to host tissue and/or cells. In accordance with the present invention, methods are provided for preventing or treating a staphylococcal infection which comprise administering an effective amount of an antibody to the surface proteins as set forth herein or their active subregions so as to treat or prevent a staphylococcal infection. In addition, these monoclonal antibodies will be useful in impairing the binding of staphylococcal bacteria to host cells

Accordingly, in accordance with the invention, administration of the antibodies of the present invention in any of the conventional ways described above (e.g., topical, parenteral, intramuscular, etc.), and will thus provide an extremely useful method of treating or preventing staphylococcal infections in human or animal patients when an effective amount of the antibody compositions are administered to a human or animal patient. By effective amount is meant that level of use, such as of an antibody titer, that will be sufficient to either prevent adherence of the bacteria, to inhibit binding of staph bacteria to host cells and thus be useful in the treatment or prevention of a staph infection. As would be recognized by one of ordinary skill in this art, the level of antibody titer needed to be effective in treating or preventing staphylococcal infection will vary depending on the nature and condition of the patient, and/or the severity of the pre-existing staphylococcal infection.

In addition to use in methods or treating or preventing a staphylococcal infection, the antibodies of the invention may also be used for the specific detection of staphylococcal proteins, or as research tools. The term "antibodies" as used herein includes monoclonal, polyclonal, chimeric, single chain, bispecific, simianized, and humanized or primatized antibodies as well as Fab fragments, such as those fragments which maintain the binding specificity of the antibodies to the

surface proteins specified above, including the products of an Fab immunoglobulin expression library. Accordingly, the invention contemplates the use of single chains such as the variable heavy and light chains of the antibodies. Generation of any of these types of antibodies or antibody fragments is well known to those skilled in the art. In the present case, antibodies to the surface proteins or their active regions as referred to above can be generated, isolated and/or purified, and then used to treat or protect against staphylococcal infection.

Any of the above described antibodies may be labeled directly with a detectable label for identification and quantification of staph bacteria. Labels for use in immunoassays are generally known to those skilled in the art and include enzymes, radioisotopes, and fluorescent, luminescent and chromogenic substances, including colored particles such as colloidal gold or latex beads. Suitable immunoassays include enzyme-linked immunosorbent assays (ELISA).

Alternatively, the antibody may be labeled indirectly by reaction with labeled substances that have an affinity for immunoglobulin. The antibody may be conjugated with a second substance and detected with a labeled third substance having an affinity for the second substance conjugated to the antibody. For example, the antibody may be conjugated to biotin and the antibody-biotin conjugate detected using labeled avidin or streptavidin. Similarly, the antibody may be conjugated to a hapten and the antibody-hapten conjugate detected using labeled anti-hapten antibody. These and other methods of labeling antibodies and assay conjugates are well known to those skilled in the art.

In accordance with the present invention, there are also provided vaccines for either active or passive immunization designed to treat or protect against staphylococcal infections, and these vaccines may be prepared from the surface proteins or their active regions as set forth above using a number of the conventional vaccine preparation methods well known in this field. In the typical vaccine, an immunogenic amount of a suitable surface protein or active fragment thereof is combined with a suitable pharmaceutically acceptable vehicle, carrier or excipient, and an amount of this vaccine effective to immunize a human or animal

patient may be administered as appropriate. By immunogenic amount it would be understood by one of ordinary skill in this art that this refers to any amount of the protein or active fragment or subregion thereof which is able to raise an immunogenic response in the human or animal patient.

In addition to active vaccines wherein antibodies are generated in the patient by virtue of the introduction or administration of an immunogenic amount of a protein or active fragment in accordance with the present invention, the isolated antibodies of the present invention, or active fragments thereof, may also be utilized in the development of vaccines for passive immunization against staph infections. In such a case, the antibody compositions as described above, namely an effective amount of the antibody and a pharmaceutically acceptable vehicle, carrier or excipient, may be administered as appropriate to a human or animal patient.

Accordingly, in accordance with the invention, the proteins or active fragments thereof may be utilized as active vaccines, and the antibodies of the invention may be used as a passive vaccine which will be useful in providing suitable antibodies to treat or prevent a staphylococcal infection. As would be recognized by one skilled in this art, a vaccine may be packaged for administration in a number of suitable ways, such as by parenteral (i.e., intramuscular, intradermal or subcutaneous) administration or nasopharyngeal (i.e., intranasal) administration. One such mode is where the vaccine is injected intramuscularly, e.g., into the deltoid muscle, however, the particular mode of administration will depend on the nature of the bacterial infection to be dealt with and the condition of the patient. The vaccine is preferably combined with a pharmaceutically acceptable vehicle, carrier or excipient to facilitate administration, and the carrier is usually water or a buffered saline, with or without a preservative. The vaccine may be lyophilized for resuspension at the time of administration or in solution.

In addition, in certain cases, the antibodies of the present invention may be modified as necessary so that, when necessary, they become less immunogenic in the patient to whom it is administered. For example, if the patient is a human, the antibody may be "humanized" by transplanting the complimentarity determining

regions of the hybridoma-derived antibody into a human monoclonal antibody as described, e.g., by Jones *et al.*, *Nature* 321:522-525 (1986) or Tempest *et al. Biotechnology* 9:266-273 (1991) or "veneered" by changing the surface exposed murine framework residues in the immunoglobulin variable regions to mimic a homologous human framework counterpart as described, e.g., by Padlan, Molecular Imm. 28:489-498 (1991), these references incorporated herein by reference. Even further, when so desired, the monoclonal antibodies of the present invention may be administered in conjunction with a suitable antibiotic to further enhance the ability of the present compositions to fight bacterial infections when necessary.

In addition to treating human or animal patients, the present compositions may also be used to halt or prevent infection of a medical device or other biomaterials such as an implant. Medical devices or polymeric biomaterials to be coated with the antibodies, proteins and active fragments described herein include, but are not limited to, staples, sutures, replacement heart valves, cardiac assist devices, hard and soft contact lenses, intraocular lens implants (anterior chamber or posterior chamber), other implants such as corneal inlays, kerato-prostheses, vascular stents, epikeratophalia devices, glaucoma shunts, retinal staples, scleral buckles, dental prostheses, thyroplastic devices, laryngoplastic devices, vascular grafts, soft and hard tissue prostheses including, but not limited to, pumps, electrical devices including stimulators and recorders, auditory prostheses, pacemakers, artificial larynx, dental implants, mammary implants, penile implants, cranio/facial tendons, artificial joints, tendons, ligaments, menisci, and disks, artificial bones, artificial organs including artificial pancreas, artificial hearts, artificial limbs, and heart valves; stents, wires, guide wires, intravenous and central venous catheters, laser and balloon angioplasty devices, vascular and heart devices (tubes, catheters, balloons), ventricular assists, blood dialysis components, blood oxygenators, urethral/ureteral/urinary devices (Foley catheters, stents, tubes and balloons), airway catheters (endotracheal and tracheostomy tubes and cuffs), enteral feeding tubes (including nasogastric, intragastric and jejunal tubes), wound drainage tubes, tubes used to drain the body cavities such as the pleural, peritoneal, cranial, and

pericardial cavities, blood bags, test tubes, blood collection tubes, vacutainers, syringes, needles, pipettes, pipette tips, and blood tubing.

It will be understood by those skilled in the art that the term "coated" or "coating", as used herein, means to apply the antibody or active fragment, or pharmaceutical composition derived therefrom, to a surface of the device, preferably an outer surface that would be exposed to streptococcal bacterial infection. The surface of the device need not be entirely covered by the protein, antibody or active fragment.

The preferred dose for administration of an antibody composition in accordance with the present invention is that amount will be effective in preventing of treating a staphylococcal infection, and one would readily recognize that this amount will vary greatly depending on the nature of the infection and the condition of a patient. As indicated above, an "effective amount" of antibody or pharmaceutical agent to be used in accordance with the invention is intended to mean a nontoxic but sufficient amount of the agent, such that the desired prophylactic or therapeutic effect is produced. As will be pointed out below, the exact amount of the antibody or a particular agent that is required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the condition being treated, the particular carrier or adjuvant being used and its mode of administration, and the like. Accordingly, the "effective amount" of any particular antibody composition will vary based on the particular circumstances, and an appropriate effective amount may be determined in each case of application by one of ordinary skill in the art using only routine experimentation. The dose should be adjusted to suit the individual to whom the composition is administered and will vary with age, weight and metabolism of the individual. The compositions may also contain stabilizers or pharmaceutically acceptable preservatives, such as thimerosal (ethyl(2-mercaptobenzoate-S)mercury sodium salt) (Sigma Chemical Company, St. Louis, MO).

When used with suitable labels or other appropriate detectable biomolecule or chemicals, the monoclonal antibodies described herein are useful for purposes

such as *in vivo* and *in vitro* diagnosis of staphylococcal infections or detection of staphylococcal bacteria. Laboratory research may also be facilitated through use of such antibodies. Various types of labels and methods of conjugating the labels to the antibodies of the invention are well known to those skilled in the art, such as the ones set forth below.

For example, the antibody can be conjugated (directly or via chelation) to a radiolabel such as, but not restricted to, ^{32}P, ^{3}H, ^{14}C, ^{35}S, ^{125}I, or ^{131}I. Detection of a label can be by methods such as scintillation counting, gamma ray spectrometry or autoradiography. Bioluminescent labels, such as derivatives of firefly luciferin, are also useful. The bioluminescent substance is covalently bound to the protein by conventional methods, and the labeled protein is detected when an enzyme, such as luciferase, catalyzes a reaction with ATP causing the bioluminescent molecule to emit photons of light. Fluorogens may also be used to label proteins. Examples of fluorogens include fluorescein and derivatives, phycoerythrin, allo-phycocyanin, phycocyanin, rhodamine, and Texas Red. The fluorogens are generally detected by a fluorescence detector.

The location of a ligand in cells can be determined by labeling an antibody as described above and detecting the label in accordance with methods well known to one skilled in the art, such as immunofluorescence microscopy using procedures such as those described by Warren et al. (*Mol. Cell. Biol.*, 7: 1326-1337, 1987).

As indicated above, the monoclonal antibodies of the present invention, or active portions or fragments thereof, are particularly useful for interfering with the initial physical interaction between a staphylococcal pathogen responsible for infection and a mammalian host, and this interference with the physical interaction may be useful both in treating patients and in preventing or reducing bacteria infection on in-dwelling medical devices to make them safer for use.

In another embodiment of the present invention, a kit which may be useful in isolating and identifying staphylococcal bacteria and infection is provided which comprises the antibodies of the present invention in a suitable form, such as lyophilized in a single vessel which then becomes active by addition of an aqueous

sample suspected of containing the staphylococcal bacteria. Such a kit will typically include a suitable container for housing the antibodies in a suitable form along with a suitable immunodetection reagent which will allow identification of complexes binding to the surface proteins or the antibodies of the invention. In general, these kits may contain an antibody in accordance with the invention and means to identify binding of that antibody when a sample from a patient is introduced to the antibody. For example, a suitable immunodetection reagent may comprise an appropriate detectable signal or label, such as a biotin or enzyme that produces a detectable color, etc., which may be linked to the antibody or utilized in other suitable ways so as to provide a detectable result when the antibody binds to the antigen.

In short, the antibodies of the present invention which recognize and bind to the surface proteins of the invention, or active fragments thereof, will thus be useful in treating a wide variety of staphylococcal infections in human and animal patients and in medical or other in-dwelling devices. In accordance with the invention, because of the nature of these proteins and the fact that they contain epitopes in common with proteins of the other type of staphylococcal bacteria, i.e., a protein from a coagulase-negative staph will raise antibodies that recognize a homologous protein from *S. aureus* and vice versa, the antibodies of the invention will exhibit cross-reactivity and should be effective against a broad range of staphylococcal infections. Accordingly, the present invention provides methods and compositions for improved methods of treating or protecting against a wide range of staphylococcal infections.

EXAMPLES

The following examples are provided which exemplify aspects of the preferred embodiments of the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventors to function well in the practice of the invention, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure,

appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

Example 1. Isolation and Sequencing of MSCRAMM's from S. Aureus

Staphylococcus aureus is known to express a class of surface-associated proteins which play important roles in pathogenicity by allowing bacteria to avoid host defenses and by acting as adhesins. These proteins are known as MSCRAMMs (Microbial Surface Components Recognizing Adhesive Matrix Molecules) and in most cases are covalently anchored to the cell wall peptidoglycan. They have several common features: (i) an N-terminal signal peptide (approximately 40 residues in length) required for Sec-dependent secretion, (ii) a wall spanning domain either rich in proline and glycine residues or composed of serine and aspartate dipeptide repeats, (iii) an LPXTG motif required for covalent anchoring of the protein to the pentaglycine crossbridge in peptidoglycan, (iv) a hydrophobic membrane-spanning domain followed by (v) several positively charged residues.

By exploiting the whole genome sequences of *S. aureus*, eight novel open reading frames encoding proteins with secretion and anchorage motifs indicative of MSCRAMMs were identified (i.e. bearing an N-terminal signal peptide and a C-terminal LPXTG motif followed by a hydrophobic domain and a positively charged tail). The following Table illustrates the list of proteins identified including their distribution among *S. aureus* genomes, their protein size and C-terminal cell wall sorting sequence.

Name	Distribution	Size	C-terminus
EkeS	ENCSJM	2189 aa	**LPNTG**SEEMDLPLKELALITGAALLA**RRR**S **KKEKE**S
DsqA	ENCSJM	~1363-2283 aa	**LPDTG**DSIKQNGLLGGVMTLLVGLGLM**KR KKKKDENDQDD**SQA
KesK	ENCSJM	~909 aa	**LPKTG**ETTSSQSWWGLYALLGMLALFIP**K FRKESK**

KrkN2	ENCSJM (Cowan)	~278 aa	**LPKTG**LTSVDNFISTVAFATLALLGSLSLLLF **KRKESK**
KrkN	ENCSJM	~661 aa	**LPQTG**EESNKDMTLPLMALIALSSIVAFVLP **RKRKN**
RkaS	ENCSJM	~801 aa	**LPKTG**TNQSSSPEAMFVLLAGIGLIATV**RR RKA**S
RrkN	NCSJM	1629 aa	**LPKTG**LESTQKGLIFSSIIGIAGLMLLA**RRRK N**
KnkA	NCSJM	629 aa	**LPKAG**ETIKEHWLPISVIVGAMGVLMIWLS **RRNKLKNKA**

Abbreviations: eMRSA-16; N, 8325; C, COL; S, MSSA; J, N315, M, Mu50.
Six out of eight are conserved in all of the six staphylococcal genomes currently sequenced and the remaining two are present in 5/6 of these genomes.

The following is a list of the DNA and protein sequences:

Ekes MRSA (SEQ ID NO:1)

acaacacagcagagaatagacaaccaggaggaaaacgaaatgaatttgttaaagaaaaataaatatagtattag
aaaatataaagtagggatattctctactttaatcgggacagttttattactttcaaacccaaatggtgcacaagctttaac
tacggatcataatgtgcaaggtggttcaaatcaagcattacctggcaactcacaaaatacaaatgccgatactaatc
gagacatagtaaatgattcgcaaaatactcctaatgcacatgcaacagacaatacatcaacaaatcaagcattgac
taatcatcaaaacgttgatgtggcaaatcaagtcgggcctgctccaatacagcctagcgcgtcgcctgcgcaaaata
ataataattctaatgctaattcaacagcaacagagccagcggcgaatacaaataataatttagcatcaaataacaat
acattaaacgtgcctaataatacagataacaatgattcagcgcgtcatctgactttaaaagaaattcaagaagatgtt
cgtcattcgtctgataagccagagttagttgcgattgctgaagaagcatctaatagaccgaaaaagagaagcagac
gtgctgcgccaacagatcctaatgcaacaccagcagatccaacggctacaccagcagatccaacggcaggaaat
ggtagtgcaccagttgcaattacagcgccatacacgccaacaactgatcccaatgccaataatataggacaaaatg
cacctaacgaagtgctttcatttgatgataacaacattagaccaagtacgaaccgttctgtgcctacagtaactgttgtt
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DsqA (8325) (SEQ ID NO:3)

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DsqA (8325) (SEQ ID NO:4)

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SDSKSMSGSTSVSDSGSLSVSTSLRKSESVSESSSLSCSQSMSDSVSTSDSSSLS
VSTSLRSSESVSESDSLSDSKSTSGSTSTSTSGSLSTSTSLSGSESVSESTSLSDS

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KesK1 (8325) (SEQ ID NO:5)

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ctaaataa

KesK1 (8325) (SEQ ID NO:6)

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NQPQATTNMSQPAQPKSSTNADQASSQPAHETNSNGNTNDKTNESSNQSDVNQ
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KrkN2 (8325) (SEQ ID NO:7)

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KrkN2 (8325) (SEQ ID NO:8)

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LNNASFWKEYKFYNANNQELATTVVNDNKKADTRTINVAVEPGYKSLTTKVHIVVP
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AFATLALLGSLSLLLFKRKESK

KrkN (8325) (SEQ ID NO:9)

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KrkN (8325) (SEQ ID NO:10)

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TVKDYAYIRFSVSNGTKAVKIVSSTHFNNKEEKYDYTLMEFAQPIYNSADKFKTEED
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TEFQNVQPTNEKMTDLQDTKYVVYESVENNESMMDTFVKHPIKTGMLNGKKYMV

METTNDDYWKDFMVEGQRVRTISKDAKNNTRTIIFPYVEGKTLYDAIVKVHVKTIDY
DGQYHVRIVDKEAFTKANTDKSNKKEQQDNSAKKEATPATPSKPTPSPVEKESQK
QDSQKDDNKQLPSVEKENDASSESGKDKTPATKPTKGEVESSSTTPTKVVSTTQ
NVAKPTTASSKTTKDVVQTSAGSSEAKDSAPLQKANIKNTNDGHTQSQNNKNTQE
NKAKSLPQTGEESNKDMTLPLMALLALSSIVAFVLPRKRKN

RkaS (COL) (SEQ ID NO:11)

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RkaS (COL) (SEQ ID NO:12)

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QGLPLSNQSKGEEMAKAMNAVGYDAMAVGNHEFDFGYDQLKKLEGMLDFPMLS
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VLQNGQIYNNDALAQTGTALANIGKITFNYRNGEVSNIKPSLINVKDVENVTPNKAL
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FSKKTDFAVTNGGGIRASIAKGKVTRYDLISVLPFGNTIAQIDVKGSDVWTAFEHSL
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KRVYHVTMNDFTASGGDGYSMFGGPREEGISLDQVLASYLKTANLAKYDTTEPQR
MLLGKPAVSEQPAKGQQGSKGSKSGKDTQPIGDDKVMDPAKKPAPGKVVLLLAH
RGTVSSGTEGSGRTIEGATVSSKSGKQLARMSVPKGSAHEKQLPKTGTNQSSSP
EAMFVLLAGIGLIATVRRRKAS

RrkN (8325) (SEQ ID NO:13)

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gaacccattaacaggtgaaaaagttggcgagggtcaaccaacagaagagatcacaaaacaaccagtagataa
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aactcatccaagtggcccagtaaatcctaacaatccaggattatcgaaagacagagcaaaaccaaatggcccagt
tcattcaatggataaaaatgataaagttaaaaaatctaaaattgctaaagaatcagtagctaatcaagagaaaaaa
cgagcagaattaccaaaaacaggtttagaaagcacgcaaaaaggtttgatctttagtagtataattggaattgctgga
ttaatgttattggctcgtagaagaaagaattaa

RrkN (8325) (SEQ ID NO:14)

SGKYGKRSMQMRDKKGPVNKRVDFLSNKLNKYSIRKFTVGTASILIGSLMYLGTQ
QEAEAAENNIENPTTLKDNVQSKEVKIEEVTNKDTAPQGVEAKSEVTSNKDTIEHE
PSVKAEDISKKEDTPKEVADVAEVQPKSSVTHNAETPKVRKARSVDEGSFDITRDS
KNVVESTPITIQGKEHFEGYGSVDIQKKPTDLGVSEVTRFNVGNESNGLIGALQLK
NKIDFSKDFNFKVRVANNHQSNTTGADGWGFLFSKGNAEEYLTNGGILGDKGLVN
SGGFKIDTGYIYTSSMDKTEKQAGQGYRGYGAFVKNDSSGNSQMVGENIDKSKT

NFLNYADNSTNTSDGKFHGQRLNDVILTYVASTGKMRAEYAGKTWETSITDLGLS
KNQAYNFLITSSQRWGLNQGINANGWMRTDLKGSEFTFTPEAPKTITELEKKVEEI
PFKKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGVIISKGEPKEEITKDPI
NELTEYGPETIAPGHRDEFDPKLPTGEKEEVPGKPGIKNPETGDVVRPPVDSVTKY
GPVKGDSIVEKEEIPFEKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGEII
SKGESKEEITKDPINELTEYGPETITPGHRDEFDPKLPTGEKEEVPGKPGIKNPETG
DVVRPPVDSVTKYGPVKGDSIVEKEEIPFEKERKFNPDLAPGTEKVTREGQKGEK
TITTPTLKNPLTGVIISKGEPKEEITKDPINELTEYGPETITPGHRDEFDPKLPTGEKE
EVPGKPGIKNPETGDVVRPPVDSVTKYGPVKGDSIVEKEEIPFKKERKFNPDLAPG
TEKVTREGQKGEKTITTPTLKNPLTGEIISKGESKEEITKDPINELTEYGPETITPGH
RDEFDPKLPTGEKEEVPGKPGIKNPETGDVVRPPVDSVTKYGPVKGDSIVEKEEIP
FEKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGEIISKGESKEEITKDPIN
ELTEYGPETITPGHRDEFDPKLPTGEKEEVPGKPGIKNPETGDVVRPPVDSVTKYG
PVKGDSIVEKEEIPFKKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGEIIS
KGESKEEITKDPINELTEYGPETITPGHRDEFDPKLPTGEKEEVPGKPGIKNPETGD
VVRPPVDSVTKYGPVKGDSIVEKEEIPFEKERKFNPDLAPGTEKVTREGQKGEKTI
TTPTLKNPLTGEIISKGESKEEITKDPINELTEYGPETITPGHRDEFDPKLPTGEKEE
VPGKPGIKNPETGDVVRPPVDSVTKYGPVKGDSIVEKEEIPFEKERKFNPDLAPGT
EKVTREGQKGEKTITTPTLKNPLTGEIISKGESKEEITKDPVNELTEFGGEKIPQGH
KDIFDPNLPTDQTEKVPGKPGIKNPDTGKVIEEPVDDVIKHGPKTGTPETKTVEIPF
ETKREFNPKLQPGEERVKQEGQPGSKTITTPITVNPLTGEKVGEGQPTEEITKQPV
DKIVEFGGEKPKDPKGPENPEKPSRPTHPSGPVNPNNPGLSKDRAKPNGPVHSM
DKNDKVKKSKIAKESVANQEKKRAELPKTGLESTQKGLIFSSIIGIAGLMLLARRRK
N

KnkA (8325) (SEQ ID NO:15)

ggaaggagtatgttgatggctaaatatcgagggaaaccgtttcaattatatgtaaagttatcgtgttcgacaatgatggc
gacaagtatcattttaacgaatatcttgccgtacgatgcccaagctgcatctgaaaaggatactgaaattacaaaaga
gatattatctaagcaagatttattagacaaagttgacaaggcaattcgtcaaattgagcaattaaaacagttatcggctt
catctaaagaacattataaagcacaactaaatgaagcgaaaacagcatcgcaaatagatgaaatcataaaacga
gctaatgagttggatagcaaagacaataaaagttctcacactgaaatgaacggtcaaagtgatatagacagtaaatt
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aagcgataaaattaatcatgctatgattgaaaaattagctaaaagtaatgcctcaacgcaacattacacatatcataa
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gaaacagatcaaaataaaatttttaatttagttaaatcggcattgaatggtaaagcggatgatttattgaatttacaaaa
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tgctgatggtaatgtatctttgcctaaagcgggggaaacgataaaagaacattggttgccgatatctgtaattgttggtg
caatgggtgtactaatgatttggttatcacgacgcaataagttgaaaaataaagcataa

KnkA (8325) (SEQ ID NO:16)

GRSMLMAKYRGKPFQLYVKLSCSTMMATSIILTNILPYDAQAASEKDTEITKEILSK
QDLLDKVDKAIRQIEQLKQLSASSKEHYKAQLNEAKTASQIDEIIKRANELDSKDNK
SSHTEMNGQSDIDSKLDQLLKDLNEVSSNVDRGQQSGEDDLNAMKNDMSQTATT
KHGEKDDKNDEAMVNKALEDLDHLNQQIHKSKDASKDTSEDPAVSTTDNNHEVA
KTPNNDGSGHVVLNKFLSNEENQSHSNRLTDKLQGSDKINHAMIEKLAKSNASTQ
HYTYHKLNTLQSLDQRIANTQLPKNQKSDLMSEVNKTKERIKSQRNIILEELARTDD
KKYATQSILESIFNKDEAVKILKDIRVDGKTDQQIADQITRHIDQLSLTTSDDLLTSLID
QSQDKSLLISQILQTKLGKAEADKLAKDWTNKGLSNRQIVDQLKKHFASTGDTSSD
DILKAILNNAKDKKQAIETILATRIERQKAKLLADLITKIETDQNKIFNLVKSALNGKAD
DLLNLQKRLNQTKKDIDYILSPIVNRPSLLDRLNKNGKTTDLNKLANLMNQGSDLLD
SIPDIPTPKPEKTLTLGKGNGLLSGLLNADGNVSLPKAGETIKEHWLPISVIVGAMG
VLMIWLSRRNKLKNKA

Primary structure analysis:

A bioinformatic approach was used for primary structure and function prediction (Figure 1). Proteins RrkN and DsqA possessed a similar structural organization to previously described MSCRAMMs. RrkN is similar in structure to the Pls/Aap proteins of *S. aureus* and *S. epidermidis*, respectively. It contains a 200-residue domain at its N-terminus showing 40% identity to Pls and Aap. The C-terminus of the protein is predominantly composed of a 128 residue repeat domain, which varies in the numbers of repeats from strain to strain. These repeats are also present in Pls and Aap. A putative *sar* homolog and *fnbpA* and *fnbpB* lie directly upstream from RrkN on the genome.

DsqA is similar in structural organization to the Sdr family of proteins. It contains a typical A domain followed by a TYYFTDVK motif which is similar to a conserved TYTFTVYVD motif found in all of the Sdr proteins. The function of this motif has yet to be determined. Two 88 residue repeat domains reside in the centre of the protein

followed by a C-terminal SX-repeat motif similar to the SD-repeat motif found in the Sdr proteins. The size of this repeat varies from strain to strain. DsqA neighbors *secY* and *secA* on the genome. A DsqA homolog (>90% identical) is also found in *S. epidermidis*.

KnkA contains no repeat domains in its sequence. Secondary structure prediction analysis indicate that this protein is predominantly composed of alpha-helices.

RkaS contains no repeat domains in its sequence. BLAST analysis indicates that it is similar to a 5' nucleotidase UDP-sugar hydrolase. The gene encoding RkaS lies directly upstream from *orfX*, the insertion site of the *mec* element.

KesK contains two 140 residue repeat domains at the N-terminus of the protein which are 38% identical. Hydropathy plot analysis (Kyte and Doolittle, 1982) indicates that there is a large hydrophilic domain in the center of the protein (residue 500-560).

EkeS contains two 300 residue repeat domains in the center of the protein which are 38% identical. Blast analysis indicates that the N-terminus of the protein (residues 1-1268, bearing both repeats) is 49% identical to FmtB, an LPXTG protein with 17 tandem repeats. FmtB is proposed to be involved indirectly in methicillin resistance as inactivation of *fmtB* abolishes methicillin resistance. This appears to be due to affecting cell wall composition as methicillin sensitivity can be relieved by increasing the production of the cell wall precursor glucosamine-1-phosphate (Komatsuzawa *et al.*, 2000).

KrkN and KrkN2 neighbor each other on the genome.

Expression analysis:

Due to lack of sequence homology with protein databases, a putative function for each of these proteins could not be predicted and hence a molecular approach was taken. Unique regions of four of the *orfs* were expressed in *E. coli* as recombinant his-tagged fusion proteins using the Qiagen pQE-30 expression system. Figure 2. represents a Coomassie stained SDS-PAGE gel of the purified N-terminal his-tag fusion proteins. The recombinant proteins RrkN1, DsqA2, KesK1 and KnkA were used to generate antibodies in rabbits. Western blotting analysis of *S. aureus* cell wall extracts revealed that KesK, KnkA and DsqA are expressed and cell wall-associated (Figure 3). Strain eMRSA-16 represents a *knkA*-negative strain since it lacks the *knkA* gene. An immunoreactive band of 65kDa reacts with the cell wall fraction from both exponential and stationary phase cells of strain 8325-4 (Figure 3, B). The absence of this band in strain eMRSA-16 suggests that it represents the gene product of *knkA*.

Western immunoblotting of the cell wall fraction of strain 8325-4 using anti-KesK antibodies identified a 150kDa immunoreactive band in both exponential and stationary phase cultures. A similar sized immunoreactive protein released from the cell wall fraction of *Lactococcus lactis* expressing full length KesK on an expression plasmid (pKS80) suggests that the 150kDa band represents the *kesK* gene product (data not shown). A *kesK* knockout mutant in *S. aureus* would be required to confirm the size of the cell wall-released KesK protein.

Western immunoblotting of the cell wall fraction of *S. aureus* strain MSSA and eMRSA-16 using anti-DsqA antibodies identified a 130kDa immunoreactive band. Expression levels are higher in stationary phase cells.

Heterologous expression in *Lactococcus lactis*:

Heterologous expression of *S. aureus* surface proteins in *Lactococcus lactis* (*L. lactis*) has previously been used as a tool to study protein function (Sinha *et al.*, 2000). In this study this surrogate system will be used to express each of the in

silico-predicted MSCRAMMs on the surface of *L. lactis* to fish for a function. KesK and KnkA have been cloned into *L. lactis* and shown by dot blotting to be surface expressed (Figure 4). No cross reaction was observed with the negative control (pKS80 plasmid without an insert) indicating that this is a specific reaction. Cell wall and protoplast fractions of *Lactococcus lactis* bearing pKS-KnkA and pKS-KesK were generated by digestion of cells with lysozyme and mutanolysin and used in Western blotting studies using anti-KnkA and anti-KesK antibodies, respectively. Unlike what was observed in *S. aureus*, KnkA was not detected in the cell wall fraction of *L. lactis* but found to be associated with the protoplast fraction. The anchoring motif of KnkA differs from the consensus LPXTG sequence in that it contains an Alanine residue instead of a Threonine (i.e. LPKAG) (Table 1). It has been recently been published that *S. aureus* contains two sortase genes, srtA and srtB (Pallen, 2001). It is possible that this variant form of the LPXTG motif is processed by the second sortase gene, which is absent in *L. lactis*. This would also explain the slight increase in size of the KnkA protein observed in the protoplast fraction, as the cell wall sorting signal has not been cleaved.

KesK was detected in the cell wall fraction of *L. lactis* but migrated at a smaller molecular weight than the KesK protein released from the cell wall of *S. aureus*. The majority of MSCRAMMs expressed on the surface of *L. lactis* are prone to proteolysis during the cell wall extraction procedure (Louise O'Brien, personal communication). Therefore, it is possible that the KesK protein released from the surface of *L. lactis* represents a truncated form of KesK. Shorter digestion times with lysozyme and mutanolysin has been shown to limit the extent of proteolysis.

Expression of in silico-predicted MSCRAMMs in vivo:

Convalescent-phase sera from 33 patients recovering from *S. aureus* infections were tested in their ability to recognize the purified N-terminal his-tag fusion proteins in an ELISA assay. Pooled sera from children and healthy blood donors were used

as negative controls. A positive reaction was taken as a value equal to or greater than twice the value of the negative control. Figures 5A-5D illustrate that all of the proteins were recognized by 27-42% of the patients suggesting that these proteins are expressed *in vivo* and are immunogenic during infection of the host.

References:

Komatsuzawa, H., Ohta, K., Sugai, M., Fujiwara, T., Glanzmann, P., Berger-Bachi, B., Suginaka, H. (2000) Tn551-mediated insertional inactivation of the *fmtB* gene encoding a cell wall-associated protein abolishes methicillin resistance in *Staphylococcus aureus*. J. Antimicrob. Chemother. **45:** 421-31.

Sinha, B., Francois, P., Que, Y.A., Hussain, M., Heilmann, C., Moreillon, P., Lew, D., Krause, K.H., Peters, G., Herrmann, M. (2000) Heterologously expressed *Staphylococcus aureus* fibronectin-binding proteins are sufficient for invasion of host cells.
Infect. Immun. **68:** 6871-6878.

Pallen, M.J., Lam, A.C., Antonio, M., Dunbar, K. (2000) An embarrassment of sortases - a richness of substrates? Trends. Microbiol. **9:** 97-101

Example 2. Isolation and Sequencing of Cross-Reactive Proteins from S. Aureus and from Coagulase-Negative Staphylococci

It has been recently shown that *S. epidermidis* contains surface proteins structurally related to *S. aureus* MSCRAMM® proteins (US 09/386,962). One protein from *S. aureus* is of particular interest since it has a close homologue in *S. epidermidis*. The protein is called DsqA or SasA (*S. aureus*) and DgsK (*S. epidermidis*). They are characterized by a typical "A" domain of approximately 500 amino acid residues,

followed by two B repeats of 88 residues that are ~40% identical, and a unique SXSX dipeptide repeat that can vary in length depending on the strain. Contained within the A domain of the *S. aureus* DsqA/SasA is a 180 residue region that has ~40% identity to a similar sized domain within region A of *S. aureus* proteins RrkN, Pls and *S. epidermidis* protein Aap The A regions of the DsqA/SasA and DgsK proteins are 46 % identical at the amino acid level, the BB repeats are 50% identical. Active and passive immunization strategies that include; vaccines, polyclonal and monoclonal antibodies recognizing both *S. aureus* and coagulase-negative staphylococcal proteins are the subject of this invention.

Specific Examples of Antibodies that Cross-React with Coagulase-Negative Staphylococci and *S. aureus*.

Coagulase-negative staphylococcal DgsK A-Domain:
Amino Acid Sequence (SEQ ID NO:17)
ASETPITSEISSNSETVANQNSTTIKNSQKETVNSTSLESNHSNSTNKQMSSEVTN
TAQSSEKAGISQQSSETSNQSSKLNTYASTDHVESTTINNDNTAQQDQNKSSNVT
SKSTQSNTSSSEKNISSNLTQSIETKATDSLATSEARTSTNQISNLTSTSTSNQSSP
TSFANLRTFSRFTVLNTMAAPTTTSTTTTSSLTSNSVVVNKDNFNEHMNLSGSATY
DPKTGIATLTPDAYSQKGAISLNTRLDSNRSFRFIGKVNLGNRYEGYSPDGVAGGD
GIGFAFSPGPLGQIGKEGAAVGIGGLNNAFGFKLDTYHNTSTPRSDAKAKADPRN
VGGGGAFGAFVSTDRNGMATTEESTAAKLNVQPTDNSFQDFVIDYNGDTKVMTV
TYAGQTFTRNLTDWIKNSGGTTFSLSMTASTGGAKNLQQVQFGTFEYTESAVAKV
RYVDANTGKDIIPPKTIAGEVDGTVNIDKQLNNFKNLGYSYVGTDALKAPNYTETSG
TPTLKLTNSSQTVIYKFKDVQ

***S. aureus* SasA A-domain:**
Amino Acid Sequence (SEQ ID NO:18)
ASDAPLTSELNTQSETVGNQNSTTIEASTSTADSTSVTKNSSSVQTSNSDTVSSEK
SEKVTSTTNSTSNQQEKLTSTSESTSSKNTTSSSDTKSVASTSSTEQPINTSTNQS
TASNNTSQSTTPSSVNLNKTSTTSTSTAPVKLRTFSRLAMSTFASAATTTAVTANTI
TVNKDNLKQYMTTSGNATYDQSTGIVTLTQDAYSQKGAITLGTRIDSNKSFHFSGK
VNLGNKYEGHGNGGDGIGFAFSPGVLGETGLNGAAVGIGGLSNAFGFKLDTYHNT
SKPNSAAKANADPSNVAGGGAFGAFVTTDSYGVATTYTSSSTADNAAKLNVQPT
NNTFQDFDINYNGDTKVMTVKYAGQTWTRNISDWIAKSGTTNFSLSMTASTGGAT
NLQQVQFGTFEYTESAVTQVRYVDVTTGKDIIPPKTYSGNVDQVVTIDNQQSALTA
KGYNYTSVDSSYASTYNDTNKTVKMTNAGQSVTYYFTDVV

The entire sequence of the Aap protein and the DNA coding therefor (with an indication of the presence of the A domain) is shown below:

***S. epidermidis* Aap Protein (A-domain underlined)** (SEQ ID NO:19)

MGKRRQGPINKKVDFLPNKLNKYSIRKFTVGTASILLGSTLIFGSSSHEAKAAEEKQ
VDPITQANQNDSSERSLENTNQPTVNNEAPQMSSTLQAEEGSNAEAPQSEPTKA
EEGGNAEAAQSEPTKAEEGGNAEAPQSEPTKAEEGGNAEAAQSEPTKTEEGSNV
KAAQSEPTKAEEGSNAEAPQSEPTKTEEGSNAKAAQSEPTKAEEGGNAEAAQSE
PTKTEEGSNAEAPQSEPTKAEEGGNAEAPQSEPTKTEEGGNAEAPNVPTIKANSD
NDTQTQFSEAPTRNDLARKEDIPAVSKNEELQSSQPNTDSKIEPTTSEPVNLNYSS
PFMSLLSMPADSSSNNTKNTIDIPPTTVKGRDNYDFYGRVDIESNPTDLNATNLTR
YNYGQPPGTTTAGAVQFKNQVSFDKDFDFNIRVANNRQSNTTGADGWGFMFSK
KDGDDFLKNGGILREKGTPSAAGFRIDTGYYNNDPLDKIQKQAGQGYRGYGTFVK
NDSQGNTSKVGSGTPSTDFLNYADNTTNDLDGKFHGQKLNNVNLKYNASNQTFT
ATYAGKTWTATLSELGLSPTDSYNFLVTSSQYGNGNSGTYASGVMRADLDGATL
TYTPKAVDGDPIISTKEIPFNKKREFDPNLAPGTEKVVQKGEPGIETTTTPTYVNPN
TGEKVGEGEPTEKITKQPVDEIVHYGGEEIKPGHKDEFDPNAPKGSQTTQPGKPG
VKNPDTGEVVTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFNPDLKPGEERVKQ
KGEPGTKTITTPTTKNPLTGEKVGEGEPTEKITKQPVDEITEYGGEEIKPGHKDEFD
PNAPKGSQEDVPGKPGVKNPGTGEVVTPPVDDVTKYGPVDGDPITSTEEIPFDKK
REFNPDLKPGEERVKQKGEPGTKTITTPTTKNPLTGEKVGEGEPTEKITKQPVDEI
VHYGGEQIPQGHKDEFDPNAPVDSKTEVPGKPGVKNPDTGEVVTPPVDDVTKYG
PVDGDSITSTEEIPFDKKREFDPNLAPGTEKVVQKGEPGTKTITTPTTKNPLTGEKV
GEGKSTEKVTKQPVDEIVEYGPTKAEPGKPAEPGKPAEPGKPAEPGKPAEPGTPAEPGKPA
EPGTPAEPGKPAEPGKPAEPGKPAEPGKPAEPGTPAEPGTPAEPGKPAEPGTPA
EPGKPAEPGTPAEPGKPAESGKPVEPGTPAQSGAPEQPNRSMHSTDNKNQLPD
TGENRQANEGTLVGSLLAIVGSLFIFGRRKKGNEK

***S. epidermidis* aap DNA** (SEQ ID NO:20)

atgggcaaac gtagacaagg tcctattaat aaaaaagtgg

attttttacc taacaaatta aacaagtatt ctataagaaa attcactgtt ggtacggcct
caatattact tggttcgaca cttatttttg gaagtagtag ccatgaagcg aaagctgcag
aagaaaaaca agttgatcca attacacaag ctaatcaaaa tgatagtagt gaaagatcac
ttgaaaacac aaatcaacct actgtaaaca atgaagcacc acagatgtct tctacattgc
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gaagcaacgc aaaagcagct caatctgagc caacgaaggc agaagaagga ggcaatgcag
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A-Domain from *S. epidermidis* Aap (amino acids 55-600) (SEQ ID NO:21)

^{55}EKQVDPITQANQNDSSERSLENTNQPTVNNEAPQMSSTLQAEEGSNAEAPQSE PTKAEEGGNAEAAQSEPTKAEEGGNAEAPQSEPTKAEEGGNAEAAQSEPTKTEE GSNVKAAQSEPTKAEEGSNAEAPQSEPTKTEEGSNAKAAQSEPTKAEEGGNAEA AQSEPTKTEEGSNAEAPQSEPTKAEEGGNAEAPQSEPTKTEEGGNAEAPNVPTIK ANSDNDTQTQFSEAPTRNDLARKEDIPAVSKNEELQSSQPNTDSKIEPTTSEPVNL NYSSPFMSLLSMPADSSSNNTKNTIDIPPTTVKGRDNYDFYGRVDIESNPTDLNAT NLTRYNYGQPPGTTTAGAVQFKNQVSFDKDFDFNIRVANNRQSNTTGADGWGF MFSKKDGDDFLKNGGILREKGTPSAAGFRIDTGYYNNDPLDKIQKQAGQGYRGYG TFVKNDSQGNTSKVGSGTPSTDFLNYADNTTNDLDGKFHGQKLNNVNLKYNASN QTFTATYAGKTWTATLSELGLSPTDSYNFLVTSSQYGNGNSGTYASGVMRADLD GA^{600}

Protein Production and Purification

Using PCR, the A domain of DgsK or SasA was amplified from the sequences described above and subcloned into the *E. coli* expression vector PQE-30 (Qiagen), which allows for the expression of a recombinant fusion protein containing six histidine residues. This vector was subsequently transformed into the *E. coli* strain ATCC 55151, grown in a 15-liter fermentor to an optical density (OD_{600}) of 0.7 and induced with 0.2 mM isopropyl-1-beta-D galactoside (IPTG) for 4 hours. The cells were harvested using an AG Technologies hollow-fiber assembly (pore size of 0.45 □m) and the cell paste frozen at –80° C. Cells were lysed in 1X PBS (10 mL of buffer/1 g of cell paste) using 2 passes through the French Press @ 1100psi. Lysed cells were spun down at 17,000rpm for 30 minutes to remove cell debris. Supernatant was passed over a 5-mL HiTrap Chelating (Pharmacia) column charged with 0.1M $NiCl_2$. After loading, the column was washed with 5 column

volumes of 10mM Tris, pH 8.0, 100mM NaCl (Buffer A). Protein was eluted using a 0-100% gradient of 10mM Tris, pH 8.0, 100mM NaCl, 200 mM imidazole (Buffer B) over 30 column volumes. SdrGN1N2N3 or SdrGN2N3 eluted at ~13% Buffer B (~26mM imidazole). Absorbance at 280nm was monitored. Fractions containing SdrGN1N2N3 or SdrGN2N3 were dialyzed in 1x PBS.

Each protein was then put through an endotoxin removal protocol. Buffers used during this protocol were made endotoxin free by passing over a 5-mL Mono-Q sepharose (Pharmacia) column. Protein was divided evenly between 4x 15mL tubes. The volume of each tube was brought to 9mL with Buffer A. 1mL of 10% Triton X-114 was added to each tube and incubated with rotation for 1 hour at 4°C. Tubes were placed in a 37°C water bath to separate phases. Tubes were spun down at 2,000rpm for 10 minutes and the upper aqueous phase from each tube was collected and the detergent extraction repeated. Aqueous phases from the 2nd extraction were combined and passed over a 5-mL IDA chelating (Sigma) column, charged with 0.1M $NiCl_2$ to remove remaining detergent. The column was washed with 9 column volumes of Buffer A before the protein was eluted with 3 column volumes of Buffer B. The eluant was passed over a 5-mL Detoxigel (Sigma) column and the flow-through collected and reapplied to the column. The flow-through from the second pass was collected and dialyzed in 1x PBS. The purified product was analyzed for concentration, purity and endotoxin level before administration into the mice.

Monoclonal Antibody Production

E. coli expressed and purified recombinant SasA and DsgK proteins were used to generate a panel of murine monoclonal antibodies while the mouse sera was used as a source of polyclonal antibodies. Briefly, a group of Balb/C or SJL mice received a series of subcutaneous immunizations of 1-10 mg of protein in solution or mixed with adjuvant as described in the Table below.

Immunization Schemes

RIMMS

Injection	Day	Amount (µg)	Route	Adjuvant
#1	0	5	Subcutaneous	FCA/RIBI
#2	2	1	Subcutaneous	FCA/RIBI
#3	4	1	Subcutaneous	FCA/RIBI
#4	7	1	Subcutaneous	FCA/RIBI
#5	9	1	Subcutaneous	FCA/RIBI

Conventional

Injection	Day	Amount (µg)	Route	Adjuvant
Primary	0	5	Subcutaneous	FCA
Boost #1	14	1	Intraperitoneal	RIBI
Boost #2	28	1	Intraperitoneal	RIBI
Boost #3	42	1	Intraperitoneal	RIBI

At the time of sacrifice (RIMMS) or seven days after a boost (conventional) serum was collected and titered in ELISA assays against MSCRAMM® proteins or on whole cells (S. *epidermidis* and *S. aureus*). Three days after the final boost, the spleens or lymph nodes were removed, teased into a single cell suspension and the lymphocytes harvested. The lymphocytes were then fused to a P3X63Ag8.653 myeloma cell line (ATCC #CRL-1580). Cell fusion, subsequent plating and feeding were performed according to the Production of Monoclonal Antibodies protocol from Current Protocols in Immunology (Chapter 2, Unit 2.).

Any clones that were generated from the fusion were then screened for specific anti-SasA antibody production using a standard ELISA assay. Positive clones were expanded and tested further for activity in a whole bacterial cell binding assay by flow cytometry and SasA binding by Biacore analysis.

Biacore Analysis

Throughout the analysis, the flow rate remained constant at 10 ml/min. Prior to the SasA or DgsK injection, test antibody was adsorbed to the chip via RAM-Fc binding. At time 0, SasA or DgsK at a concentration of 30 mg/ml was injected over the chip for 3 min followed by 2 minutes of dissociation. This phase of the analysis

measured the relative association and disassociation kinetics of the Mab / SasA or DgsK interaction.

Binding to Whole Bacteria

Bacterial samples *S. aureus* Newman, *S. aureus* 67-0, *S. aureus* 397 (Sal6), *S. aureus* Wood, *S. aureus* 8325-4, methicillin resistant *S. aureus* MRSA 16, *S. epidermidis* ATCC 35984, *S. epidermidis* HB, *S. epidermidis* CN-899 and *S. haemolyticus* ATCC 43253 were collected, washed and incubated with Mab or PBS alone (control) at a concentration of 2 µg/ml after blocking with rabbit IgG (50 mg/ml). Following incubation with antibody, bacterial cells were incubated with Goat-$F_{(ab')2}$-Anti-Mouse-$F_{(ab')2}$-FITC which served as the detection antibody. After antibody labeling, bacterial cells were aspirated through the FACScaliber flow cytometer to analyze fluorescence emission (excitation: 488, emission: 570). For each bacterial strain, 10,000 events were collected and measured. These data indicate that antibodies against *S. aureus* SasA were able to recognize a homologous protein on the surface of coagulase-negative staphylococci. The data support Western blot analysis demonstrating that rabbit polyclonal antibodies against *S. aureus* SasA cross-react with a protein released from the cell surface of *S. epidermidis* HB as well as the recombinant A-region from DsgK cloned from *S. epidermidis* (see Table below and Figure 6).

Polyclonal Sera Reactivity

	Newman	67-0	397 (SAL6)	Wood 46	8325-4	MRSA 16	ATCC 35984	HB	CN-899	ATCC 43253
Normal Mouse Sera	-	-	-	-	-	-	-	-	-	-
Mouse anti-SasA	+	+	+/-	-	+	+	+	+	+	+

What is claimed is:

1. An isolated antibody which binds to a staphylococcal surface protein selected from the group consisting of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21.

2. The antibody according to Claim 1 wherein the antibody is raised against the A domain of the surface protein.

3. The antibody according to Claim 1, wherein the antibody treats or prevents *S. aureus* infection in a human or animal.

4. The antibody according to Claim 1, wherein the antibody is suitable for parenteral, oral, intranasal, subcutaneous, aerosolized or intravenous administration in a human or animal.

5. The antibody according to Claim 1, wherein said antibody is a monoclonal antibody.

6. The antibody according to Claim 1, wherein said antibody is a polyclonal antibody.

7. The antibody according to Claim 5 wherein the monoclonal antibody is of a type selected from the group consisting of murine, chimeric, humanized and human monoclonal antibodies.

8. The antibody according to Claim 5 wherein the antibody is a single chain monoclonal antibody.

9. The antibody according to Claim 1 which comprises an antibody fragment having the same binding specificity of an antibody which binds to a staphylococcal surface protein having the sequence selected from the group consisting of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21.

10. The antibody according to Claim 1 that is raised against a protein having an amino acid sequence selected from the group consisting of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21.

11. The antibody according to Claim 1 wherein the surface protein has an amino acid sequence encoded by a nucleic acid sequence selected from the group consisting of nucleic acid sequences SEQ ID NOS. 1, 3, 5, 7, 9, 11, 13, 15, 20 and the nucleic acid sequences coding for the A domain of the Aap protein or degenerates thereof.

12. Isolated antisera containing an antibody according to Claim 1.

13. A diagnostic kit comprising an antibody according to Claim 1 and means for detecting binding by that antibody.

14. A diagnostic kit according to Claim 13 wherein said means for detecting binding comprises a detectable label that is linked to said antibody.

15. A method of diagnosing an infection of *S. aureus* comprising adding an antibody according to Claim 1 to a sample suspected of being infected with *S. aureus*, and determining if antibodies have bound to the sample.

16. A pharmaceutical composition for treating or preventing an infection of *S. aureus* comprising an effective amount of the antibody of Claim 1 and a pharmaceutically acceptable vehicle, carrier or excipient.

17. A method of treating or preventing an infection of *S. aureus* comprising administering to a human or animal patient an effective amount of an antibody according to Claim 1.

18. A method of inducing an immunological response comprising administering to a human or animal an immunogenic amount of an isolated protein selected from the group consisting of the amino acid sequences SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21.

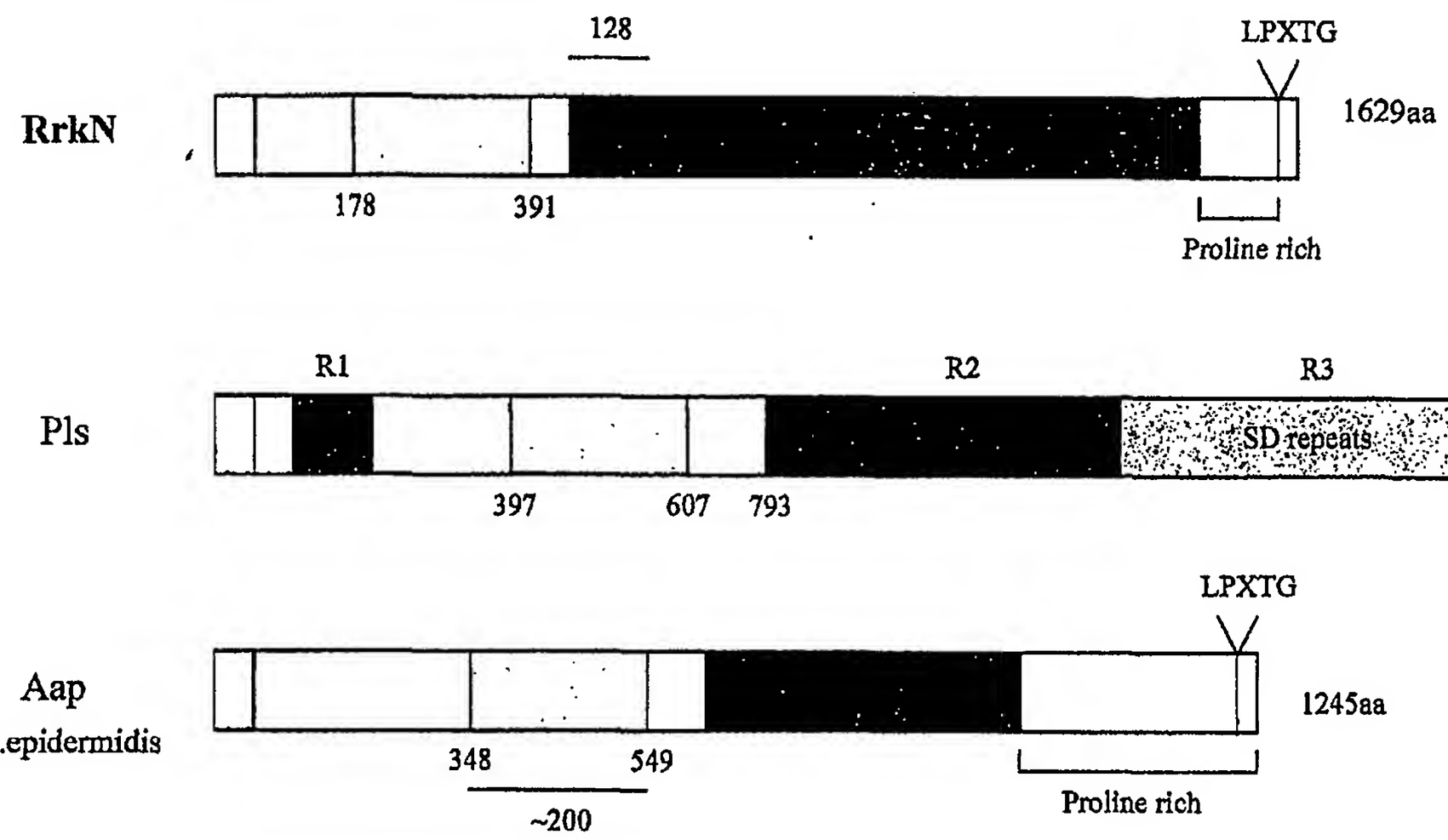
19. An isolated antibody according to Claim 1 that has the ability to bind to an amino acid sequence coded by the nucleic acid sequence of SEQ ID NOS. 1, 3, 5, 7, 9, 11, 13, 15, 20 and the nucleic acid sequences coding for the A domain of the Aap protein or degenerates thereof.

20. An isolated active fragment from the A domain of the DsqA protein.

21. An isolated antibody according to Claim 1 further comprising a physiologically acceptable antibiotic.

22. A vaccine for treating or preventing an infection of *S. aureus* comprising an amount of a protein sequence selected from the group consisting of SEQ ID NOS. 2, 4, 6, 8, 10, 12, 14, 16, 17, 18, 19 and 21 in an amount effective to elicit an immune response, and a pharmaceutically acceptable vehicle, carrier or excipient.

Figure 1. Primary structure of in silico-predicted LPXTG proteins.



Anti-adhesin, associated with the mec element

Proposed to be involved in biofilm formation

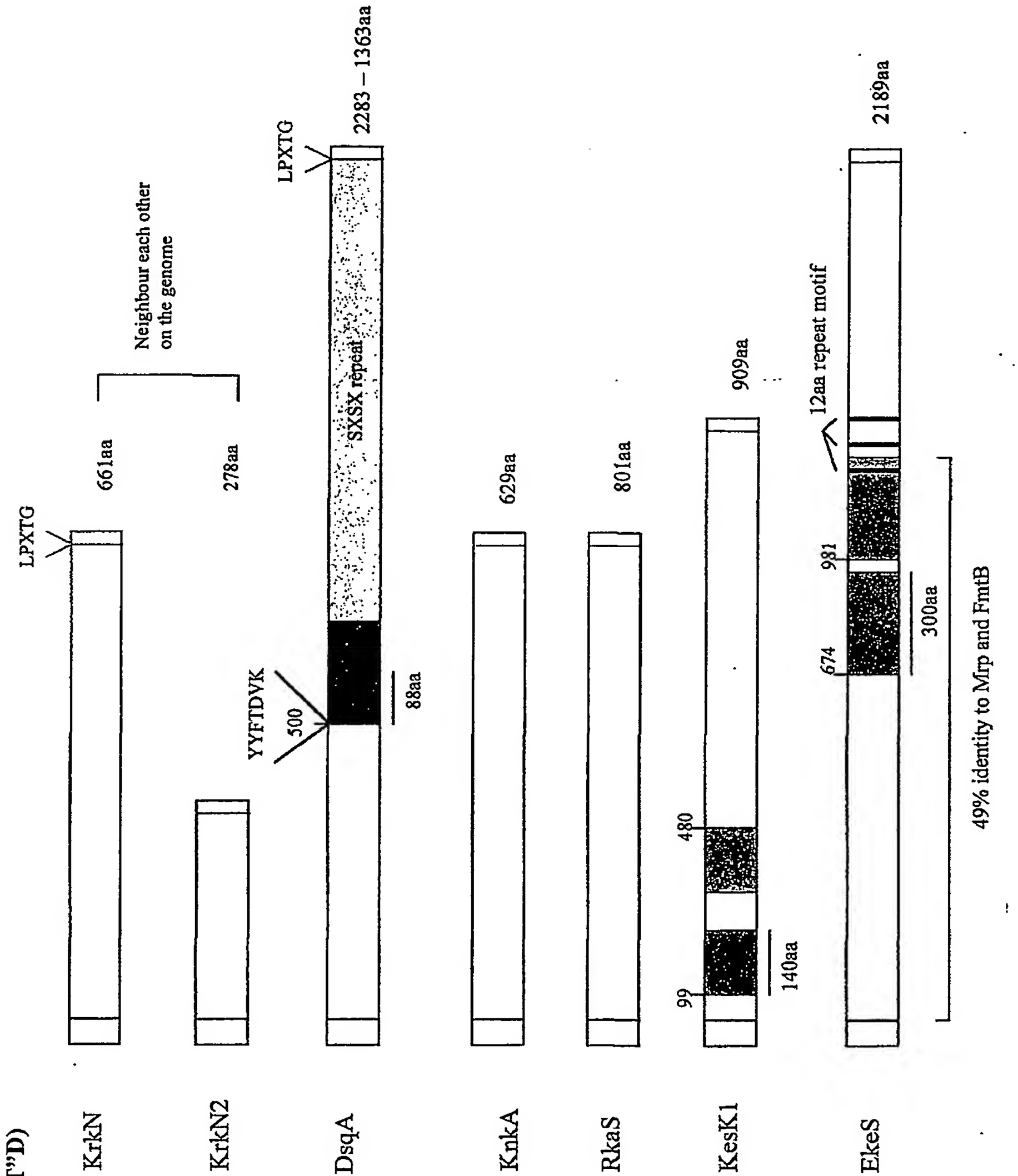
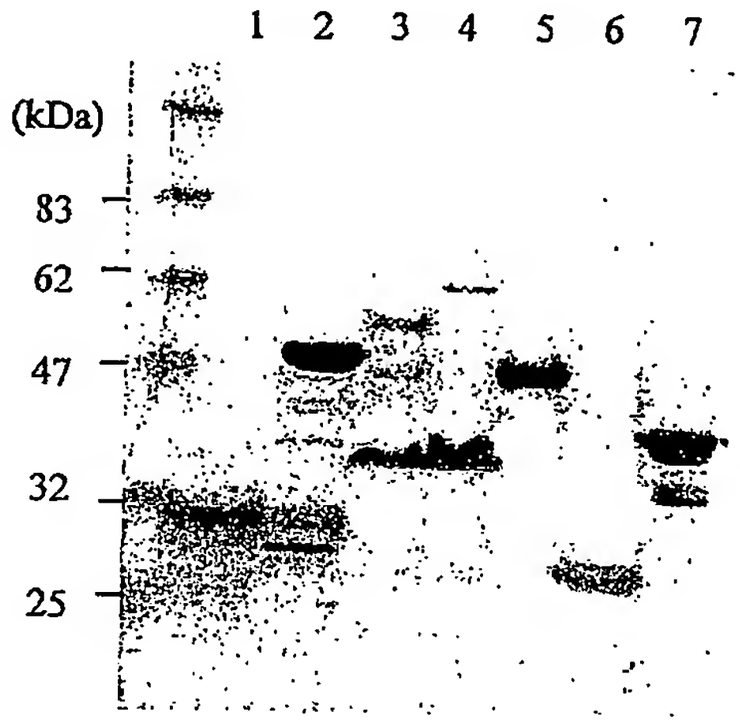


Figure 1 (CONT"D)



		Residues	Predicted MW	Apparent MW
•	**RrkN 1**	60 - 215	19	29
•	**RrkN 2**	60 - 437	45	48
•	**DsqA 1**	54 - 279	27	38
•	**DsqA 2**	54 - 533	58	62
•	**KesK 1**	55 - 335	34	47
•	**KnkA**	39 - 210	20	27
•	**KesK 2**	329 - 591	31	40

Figure 2. Coomassie gel of the purified N-terminal His-tagged fusion proteins.

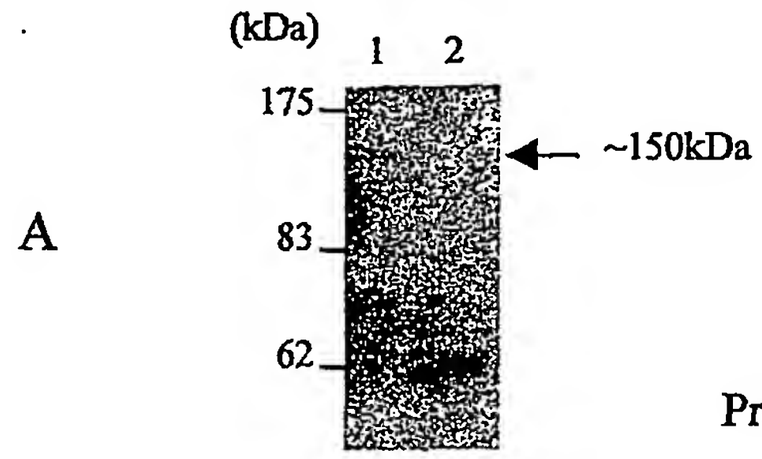


Figure 3. Western blotting of *S.aureus* cell wall extracts. Bacterial cells were standardised to an OD_{600} of 50 units and cell walls were isolated by lysostaphin digestion of stabilised protoplasts.
A. Lane 1, 8325-4 (early exponential phase); lane 2, 8325-4 (stationary phase).
B. Lanes 1 and 2, eMRSA-16 ; lanes 3 and 4, 8325-4; lanes 1 and 3 represent early exponential phase cells and lanes 2 and 4 represent stationary phase cells.
C. Lanes 1 and 2, MSSA ; lanes 3 and 4, eMRSA-16; lanes 1 and 3 represent early exponential phase cells and lanes 2 and 4 represent stationary phase cells.

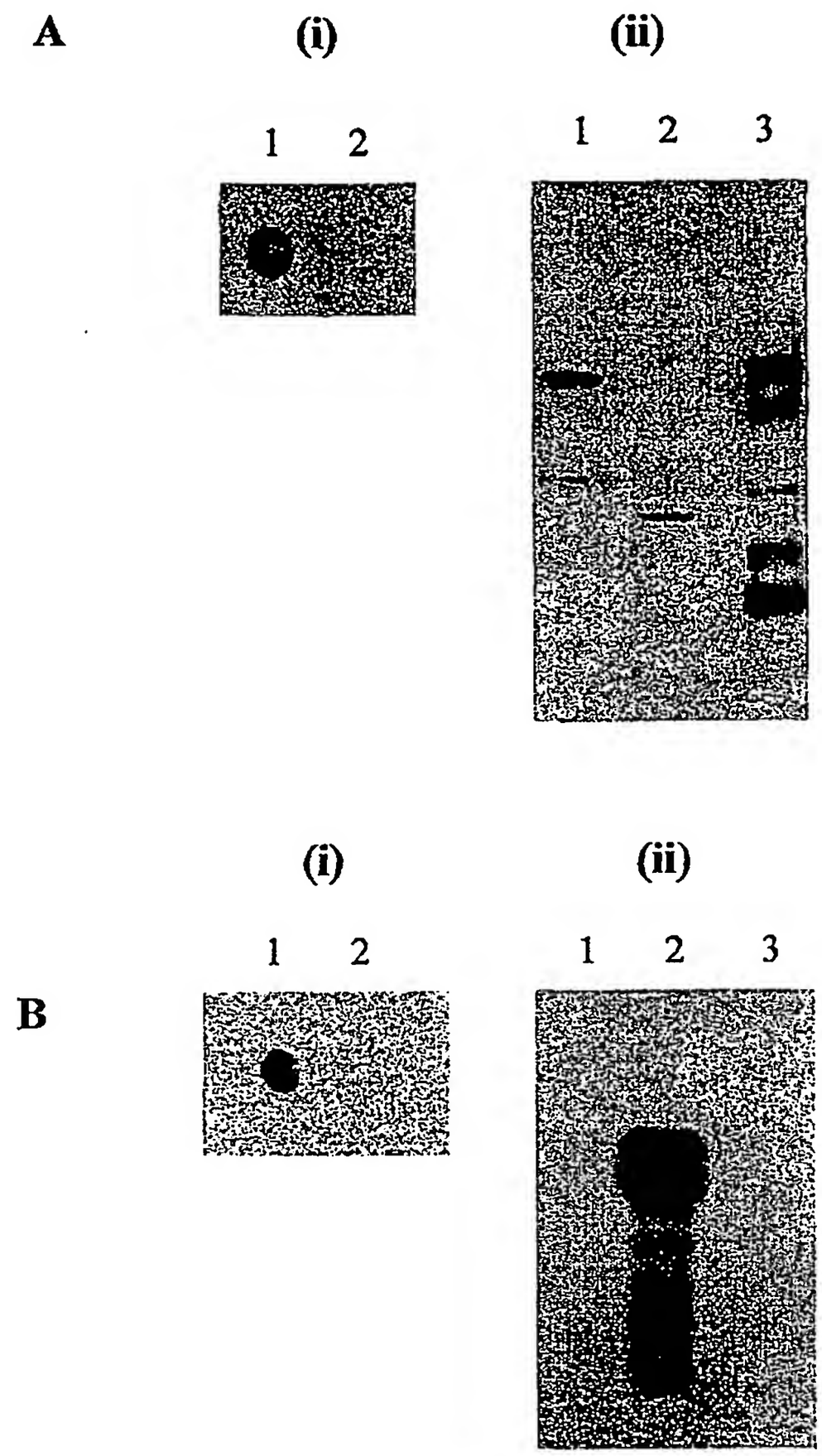


Figure 4. Dot blotting and Western immunoblotting of *Lactococcus lactis* expressing *S.aureus* MSCRAMMs. Full length *knkA* and *kesK* were cloned into the *L.lactis* expression plasmid pKS80 and electroporated into compotent *L.lactis* MG1363 cells. Positive KnkA and KesK expressing clones were detected using dot blotting with anti-KnkA (A) and anti-KesK (B) antibodies, respectively. *L.lactis* bearing pKS80 was used as a negative control. A.(i) lane 1, *L.lactis* pKS-KnkA; lane 2, *L.lactis* pKS80. B. (ii) lane 1, *L.lactis* pKS-KesK; lane 2, *L.lactis* pKS80. Western immunoblotting was used to examine the expression of KesK and KnkA in *S.aureus* and *L.lactis*. A (ii). Lane 1, cell wall extract from exponential phase *S.aureus* strain 8325-4, lane 2, protoplast fraction from *L.lactis* bearing pKS80; lane 3, protoplast fraction from *L.lactis* bearing pKS-KnkA. B. (ii) Lane 1, cell wall extract from exponential phase *S.aureus* strain 8325-4; lane 2, cell wall extract from *L.lactis* bearing pKS-KesK; lane 3, cell wall extract from *L.lactis* bearing pKS80.

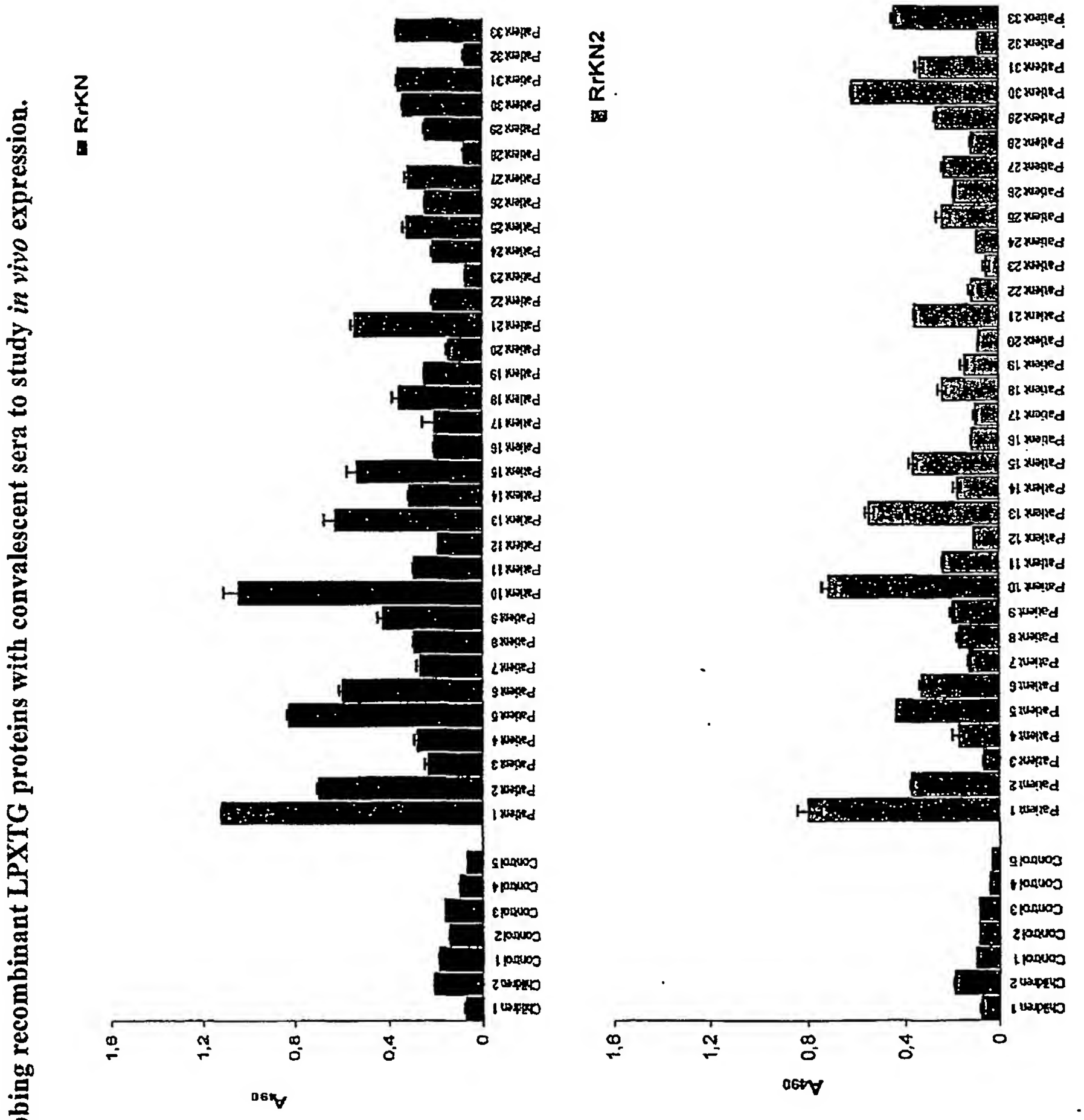
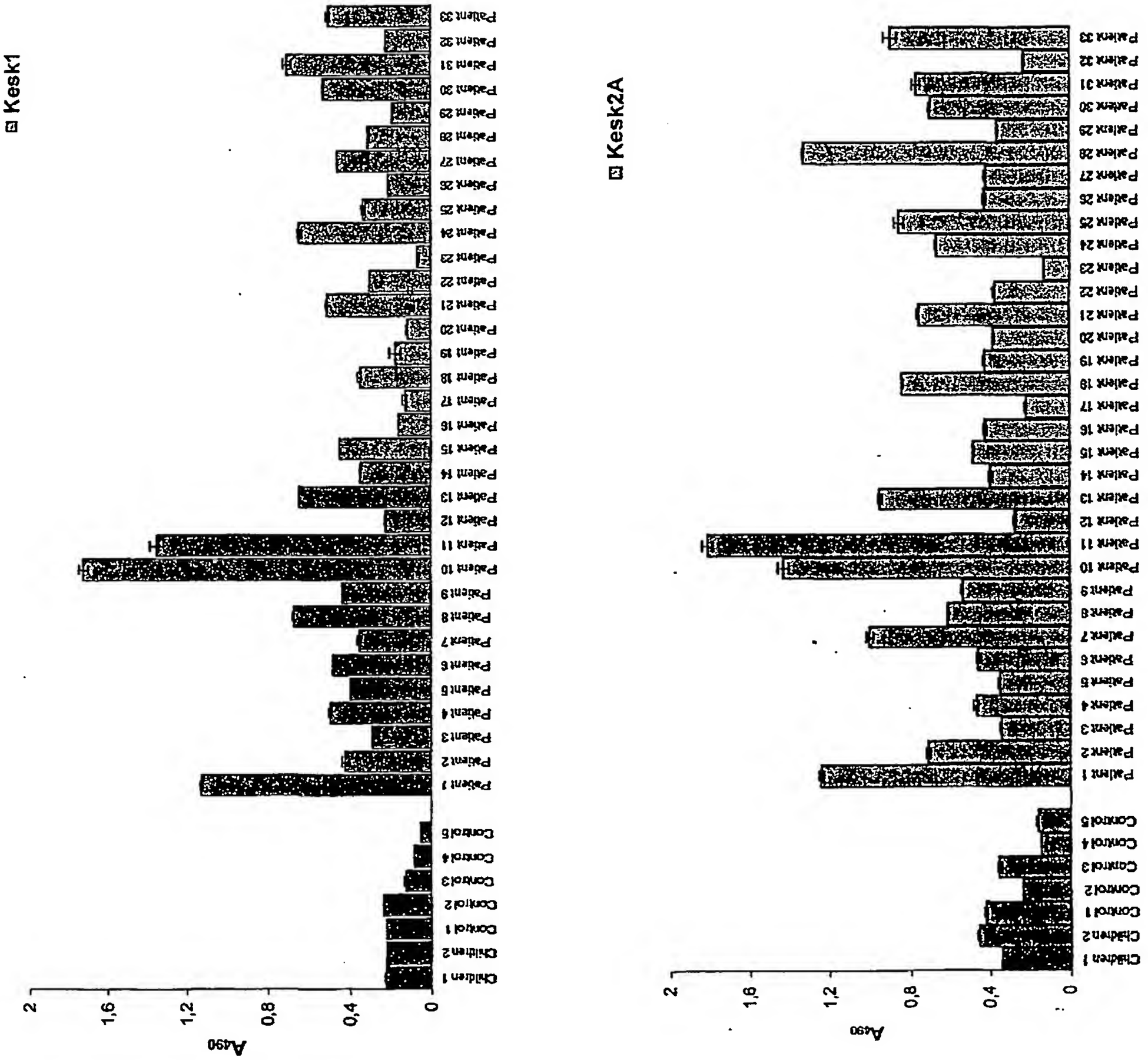


Figure 5A. Probing recombinant LPXTG proteins with convalescent sera to study *in vivo* expression.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Patient 14
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Patient 12
Patient 11
Patient 10
Patient 9
Patient 8
Patient 7
Patient 6
Patient 5
Patient 4
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Patient 2
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Control 2
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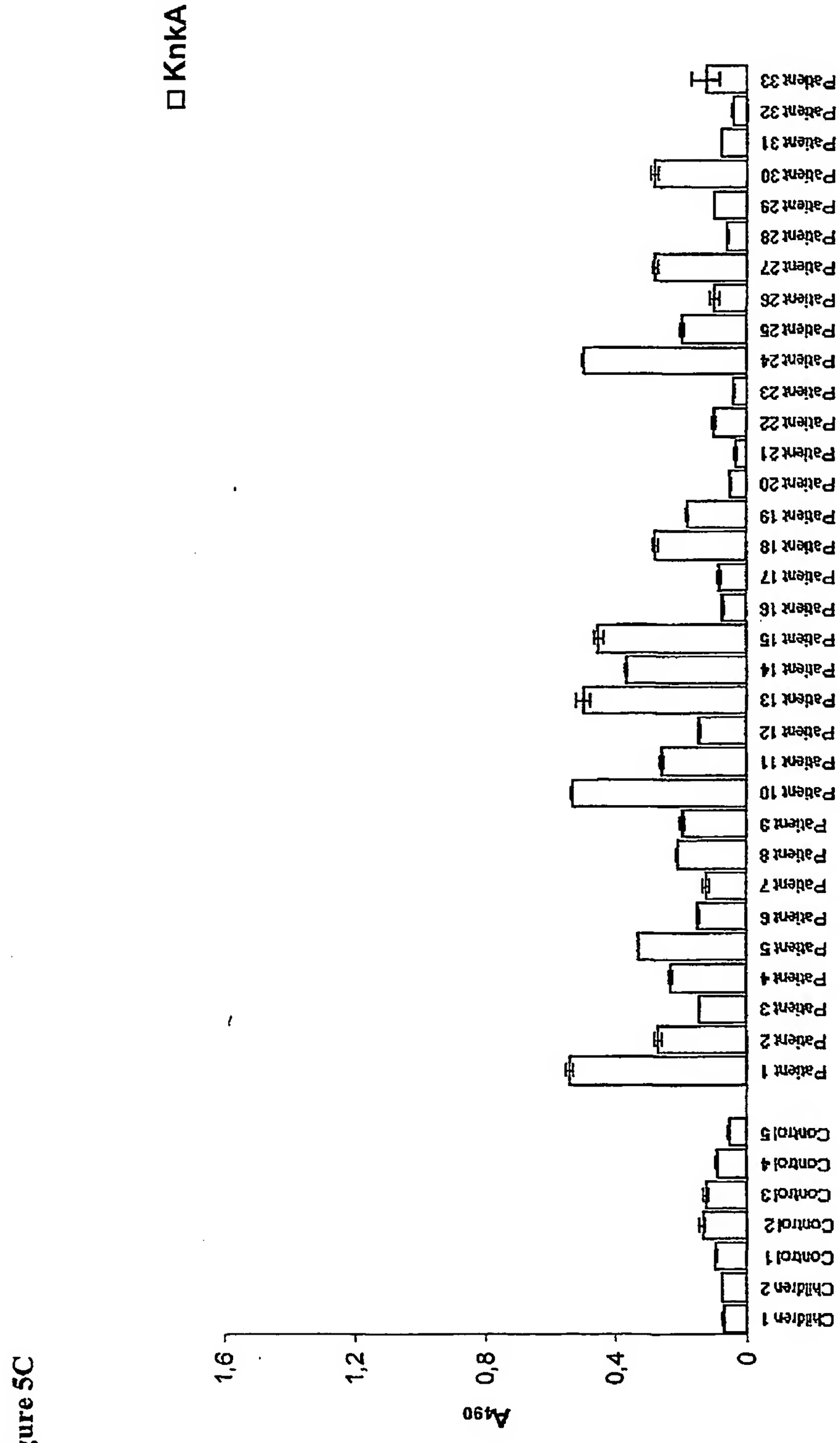
Figure 5B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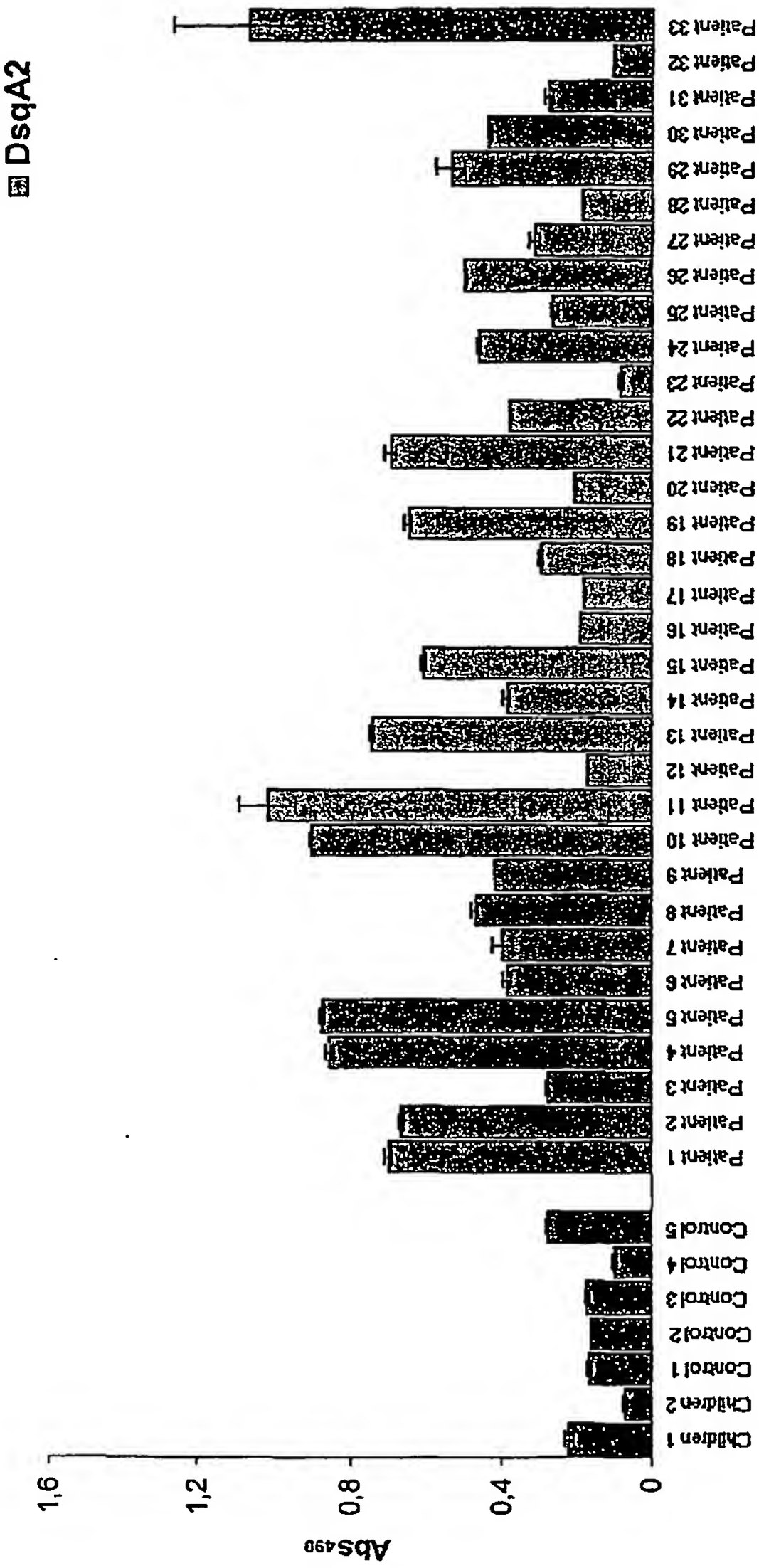
1,6

Figure 5C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Patient 11
Patient 10
Patient 9
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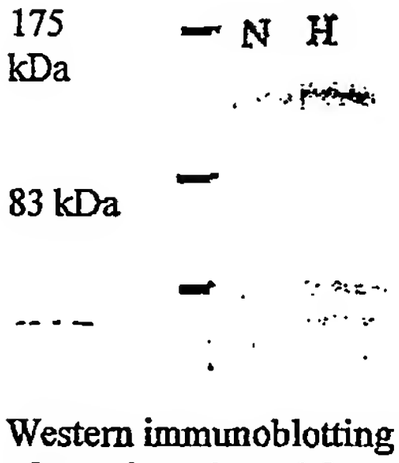
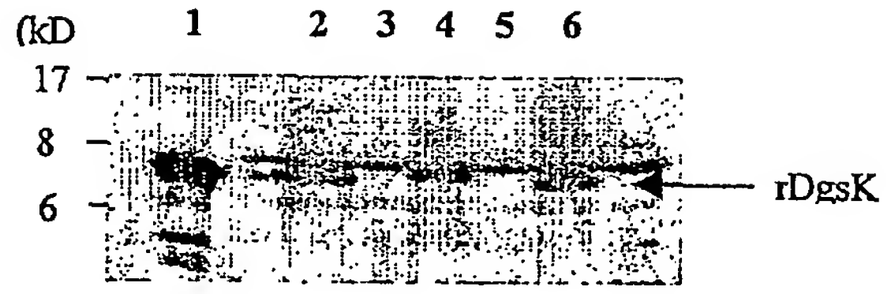
Figure 5D



Western immunoblotting analysis of proteins released from the cell wall of *S. aureus* Newman (N) and *S. epidermidis* HB (H). Probed with rabbit anti-*S. aureus* SasA region A antibodies and goat anti-rabbit conjugated to horseradish peroxidase



Cross reaction of *S. aureus* SasA A-region antibodies with DgsK expressed in *E. coli*. Lane 1, FPLC purified SasA A-region control. Lanes 2, 4 and 6, DgsK A-region expressed from pQE-30 in *E. coli* strain TOPP-3 (induced); lanes 3, 5 and 7, TOPP-3 bearing pQE-30 with *dgsK* insert (uninduced).

FIGURE 6

SEQUENCE LISTING

<110> FOSTER, Timothy

<120> CROSS-REACTIVE MONOCLONAL AND POLYCLONAL ANTIBODIES. . .

<130> P07263US01/BAS

<150> US 60/298,098
<151> 2001-06-15

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Val Ala Asn Gln Val Gly Pro Ala Pro Ile Gln Pro Ser Ala Ser Pro
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ccttcacttg taaaatcaga tacaaatgat gcagtagtaa cgaatgatca atcaagttca 780
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gataattggc gaccaattga ttttcaaatg aaaaatgata aaggtgaaag acagttctat 1140
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catgtcagaa ttataaatca ggatatcaat acaaaagatg atgatacatc acaaaataac 2040
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gctgaaaata gcagcactgc aacaaatcct aaagatgcgt ctgataaagc agatgtgata 2160

gaaccagagt ctgacgtggt taaagatgct gataataata ttgataaaga tgtgcaacat 2220

gatgttgatc atttatccga tatgtcggat aataatcact tcgataaata tgatttaaaa 2280

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gtcatacagc tgaatcatat tgccgataaa aataatcata ctggaaaagc agcaaagctt 2460

gacgtagtga aacaaaatta taataataca gacaaagtta ctgacaaaaa aacaactgaa 2520

catctgccga gtgatattca taaaactgta gataaaacag tgaaaacaaa agaaaaagcc 2580

ggcacaccat cgaaagaaaa caaacttagt caatctaaaa tgctaccaaa aactggagaa 2640

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attcctaaat tcagaaaaga atctaaataa 2730

<210> 6
<211> 909
<212> PRT
<213> Staphylococcus epidermidis

<400> 6

Leu Leu Ser Ile Lys Tyr Asn Leu Ile Gly Val Val Asn Asn Met Asn
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Lys His His Pro Lys Leu Arg Ser Phe Tyr Ser Ile Arg Lys Ser Thr
20 25 30

Leu Gly Val Ala Ser Val Ile Val Ser Thr Leu Phe Leu Ile Thr Ser
35 40 45

Gln His Gln Ala Gln Ala Ala Glu Asn Thr Asn Thr Ser Asp Lys Ile
50 55 60

Ser Glu Asn Gln Asn Asn Asn Ala Thr Thr Thr Gln Pro Pro Lys Asp
65 70 75 80

Thr Asn Gln Thr Gln Pro Ala Thr Gln Pro Ala Asn Thr Ala Lys Asn
85 90 95

Tyr Pro Ala Ala Asp Glu Ser Leu Lys Asp Ala Ile Lys Asp Pro Ala
100 105 110

Leu Glu Asn Lys Glu His Asp Ile Gly Pro Arg Glu Gln Val Asn Phe
115 120 125

Gln Leu Leu Asp Lys Asn Asn Glu Thr Gln Tyr Tyr His Phe Phe Ser
130 135 140

Ile Lys Asp Pro Ala Asp Val Tyr Tyr Thr Lys Lys Lys Ala Glu Val
145 150 155 160

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Glu Leu Asp Ile Asn Thr Ala Ser Thr Trp Lys Lys Phe Glu Val Tyr
                165                 170                 175

Glu Asn Asn Gln Lys Leu Pro Val Arg Leu Val Ser Tyr Ser Pro Val
            180                 185                 190

Pro Glu Asp His Ala Tyr Ile Arg Phe Pro Val Ser Asp Gly Thr Gln
        195                 200                 205

Glu Leu Lys Ile Val Ser Ser Thr Gln Ile Asp Asp Gly Glu Glu Thr
    210                 215                 220

Asn Tyr Asp Tyr Thr Lys Leu Val Phe Ala Lys Pro Ile Tyr Asn Asp
225                 230                 235                 240

Pro Ser Leu Val Lys Ser Asp Thr Asn Asp Ala Val Val Thr Asn Asp
                245                 250                 255

Gln Ser Ser Ser Val Ala Ser Asn Gln Thr Asn Thr Asn Thr Ser Asn
            260                 265                 270

Gln Asn Ile Ser Thr Ile Asn Asn Ala Asn Asn Gln Pro Gln Ala Thr
        275                 280                 285

Thr Asn Met Ser Gln Pro Ala Gln Pro Lys Ser Ser Thr Asn Ala Asp
    290                 295                 300

Gln Ala Ser Ser Gln Pro Ala His Glu Thr Asn Ser Asn Gly Asn Thr
305                 310                 315                 320

Asn Asp Lys Thr Asn Glu Ser Ser Asn Gln Ser Asp Val Asn Gln Gln
                325                 330                 335

Tyr Pro Pro Ala Asp Glu Ser Leu Gln Asp Ala Ile Lys Asn Pro Ala
            340                 345                 350

Ile Ile Asp Lys Glu His Thr Ala Asp Asn Trp Arg Pro Ile Asp Phe
        355                 360                 365

Gln Met Lys Asn Asp Lys Gly Glu Arg Gln Phe Tyr His Tyr Ala Ser
    370                 375                 380

Thr Val Glu Pro Ala Thr Val Ile Phe Thr Lys Thr Gly Pro Ile Ile
385                 390                 395                 400

Glu Leu Gly Leu Lys Thr Ala Ser Thr Trp Lys Lys Phe Glu Val Tyr
                405                 410                 415

Glu Gly Asp Lys Lys Leu Pro Val Glu Leu Val Ser Tyr Asp Ser Asp
            420                 425                 430

Lys Asp Tyr Ala Tyr Ile Arg Phe Pro Val Ser Asn Gly Thr Arg Glu
        435                 440                 445

Val Lys Ile Val Ser Ser Ile Glu Tyr Gly Glu Asn Ile His Glu Asp
    450                 455                 460

Tyr Asp Tyr Thr Leu Met Val Phe Ala Gln Pro Ile Thr Asn Asn Pro
465                 470                 475                 480
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Asp Asp Tyr Val Asp Glu Glu Thr Tyr Asn Leu Gln Lys Leu Leu Ala
                485                 490                 495

Pro Tyr His Lys Ala Lys Thr Leu Glu Arg Gln Val Tyr Glu Leu Glu
            500                 505                 510

Lys Leu Gln Glu Lys Leu Pro Glu Lys Tyr Lys Ala Glu Tyr Lys Lys
        515                 520                 525

Lys Leu Asp Gln Thr Arg Val Glu Leu Ala Asp Gln Val Lys Ser Ala
    530                 535                 540

Val Thr Glu Phe Glu Asn Val Thr Pro Thr Asn Asp Gln Leu Thr Asp
545                 550                 555                 560

Leu Gln Glu Ala His Phe Val Val Phe Glu Ser Glu Glu Asn Ser Glu
                565                 570                 575

Ser Val Met Asp Gly Phe Val Glu His Pro Phe Tyr Thr Ala Thr Leu
            580                 585                 590

Asn Gly Gln Lys Tyr Val Val Met Lys Thr Lys Asp Asp Ser Tyr Trp
        595                 600                 605

Lys Asp Leu Ile Val Glu Gly Lys Arg Val Thr Thr Val Ser Lys Asp
    610                 615                 620

Pro Lys Asn Asn Ser Arg Thr Leu Ile Phe Pro Tyr Ile Pro Asp Lys
625                 630                 635                 640

Ala Val Tyr Asn Ala Ile Val Lys Val Val Val Ala Asn Ile Gly Tyr
                645                 650                 655

Glu Gly Gln Tyr His Val Arg Ile Ile Asn Gln Asp Ile Asn Thr Lys
            660                 665                 670

Asp Asp Asp Thr Ser Gln Asn Asn Thr Ser Glu Pro Leu Asn Val Gln
        675                 680                 685

Thr Gly Gln Glu Gly Lys Val Ala Asp Thr Asp Val Ala Glu Asn Ser
    690                 695                 700

Ser Thr Ala Thr Asn Pro Lys Asp Ala Ser Asp Lys Ala Asp Val Ile
705                 710                 715                 720

Glu Pro Glu Ser Asp Val Val Lys Asp Ala Asp Asn Asn Ile Asp Lys
                725                 730                 735

Asp Val Gln His Asp Val Asp His Leu Ser Asp Met Ser Asp Asn Asn
            740                 745                 750

His Phe Asp Lys Tyr Asp Leu Lys Glu Met Asp Thr Gln Ile Ala Lys
        755                 760                 765

Asp Thr Asp Arg Asn Val Asp Lys Asp Ala Asp Asn Ser Val Gly Met
    770                 775                 780

Ser Ser Asn Val Asp Thr Asp Lys Asp Ser Asn Lys Asn Lys Asp Lys
785                 790                 795                 800
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Val Ile Gln Leu Asn His Ile Ala Asp Lys Asn Asn His Thr Gly Lys
805 810 815

Ala Ala Lys Leu Asp Val Val Lys Gln Asn Tyr Asn Asn Thr Asp Lys
820 825 830

Val Thr Asp Lys Lys Thr Thr Glu His Leu Pro Ser Asp Ile His Lys
835 840 845

Thr Val Asp Lys Thr Val Lys Thr Lys Glu Lys Ala Gly Thr Pro Ser
850 855 860

Lys Glu Asn Lys Leu Ser Gln Ser Lys Met Leu Pro Lys Thr Gly Glu
865 870 875 880

Thr Thr Ser Ser Gln Ser Trp Trp Gly Leu Tyr Ala Leu Leu Gly Met
885 890 895

Leu Ala Leu Phe Ile Pro Lys Phe Arg Lys Glu Ser Lys
900 905

<210> 7
<211> 1065
<212> DNA
<213> Staphylococcus epidermidis

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ataggcgcag acagccaaca agtcaatgcg gcaacagaag ctacgaacgc aactaataat 180

caaagcacac aagtttctca agcaacatca caaccaatta atttccaagt gcaaaaagat 240

ggctcttcag agaagtcaca catggatgac tatatgcaac accctggtaa agtaattaaa 300

caaaataata aatattattt ccaaaccgtg ttaaacaatg catcattctg gaaagaatac 360

aaattttaca atgcaaacaa tcaagaatta gcaacaactg ttgttaacga taataaaaaa 420

gcggatacta gaacaatcaa tgttgcagtt gaacctggat ataagagctt aactactaaa 480

gtacatattg tcgtgccaca aattaattac aatcatagat atactacgca tttggaattt 540

gaaaaagcaa ttcctacatt agctgacgca gcaaaaccaa acaatgttaa accggttcaa 600

ccaaaaccag ctcaacctaa aacacctact gagcaaacta aaccagttca acctaaagtt 660

gaaaaagtta aacctactgt aactacaaca agcaaagttg aagacaatca ctctactaaa 720

gttgtaagta ctgacacaac aaaagatcaa actaaaacac aaactgctca tacagttaaa 780

acagcacaaa ctgctcaaga acaaaataaa gttcaaacac ctgttaaaga tgttgcaaca 840

gcgaaatctg aaagcaacaa tcaagctgta agtgataata aatcacaaca aactaacaaa 900

gttacaaaac ataacgaaac gcctaaacaa gcatctaaag ctaaagaatt accaaaaact 960

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ggttcattat ctttattact tttcaaaaga aaagaatcta ataa 1065

<210> 8
<211> 354
<212> PRT
<213> Staphylococcus epidermidis

<400> 8

Glu Glu Asn Asn Met Thr Lys His Tyr Leu Asn Ser Lys Tyr Gln Ser
1 5 10 15

Glu Gln Arg Ser Ser Ala Met Lys Lys Ile Thr Met Gly Thr Ala Ser
20 25 30

Ile Ile Leu Gly Ser Leu Val Tyr Ile Gly Ala Asp Ser Gln Gln Val
35 40 45

Asn Ala Ala Thr Glu Ala Thr Asn Ala Thr Asn Asn Gln Ser Thr Gln
50 55 60

Val Ser Gln Ala Thr Ser Gln Pro Ile Asn Phe Gln Val Gln Lys Asp
65 70 75 80

Gly Ser Ser Glu Lys Ser His Met Asp Asp Tyr Met Gln His Pro Gly
85 90 95

Lys Val Ile Lys Gln Asn Asn Lys Tyr Tyr Phe Gln Thr Val Leu Asn
100 105 110

Asn Ala Ser Phe Trp Lys Glu Tyr Lys Phe Tyr Asn Ala Asn Asn Gln
115 120 125

Glu Leu Ala Thr Thr Val Val Asn Asp Asn Lys Lys Ala Asp Thr Arg
130 135 140

Thr Ile Asn Val Ala Val Glu Pro Gly Tyr Lys Ser Leu Thr Thr Lys
145 150 155 160

Val His Ile Val Val Pro Gln Ile Asn Tyr Asn His Arg Tyr Thr Thr
165 170 175

His Leu Glu Phe Glu Lys Ala Ile Pro Thr Leu Ala Asp Ala Ala Lys
180 185 190

Pro Asn Asn Val Lys Pro Val Gln Pro Lys Pro Ala Gln Pro Lys Thr
195 200 205

Pro Thr Glu Gln Thr Lys Pro Val Gln Pro Lys Val Glu Lys Val Lys
210 215 220

Pro Thr Val Thr Thr Thr Ser Lys Val Glu Asp Asn His Ser Thr Lys
225 230 235 240

Val Val Ser Thr Asp Thr Thr Lys Asp Gln Thr Lys Thr Gln Thr Ala
245 250 255

His Thr Val Lys Thr Ala Gln Thr Ala Gln Glu Gln Asn Lys Val Gln

260 265 270

Thr Pro Val Lys Asp Val Ala Thr Ala Lys Ser Glu Ser Asn Asn Gln
275 280 285

Ala Val Ser Asp Asn Lys Ser Gln Gln Thr Asn Lys Val Thr Lys His
290 295 300

Asn Glu Thr Pro Lys Gln Ala Ser Lys Ala Lys Glu Leu Pro Lys Thr
305 310 315 320

Gly Leu Thr Ser Val Asp Asn Phe Ile Ser Thr Val Ala Phe Ala Thr
325 330 335

Leu Ala Leu Leu Gly Ser Leu Ser Leu Leu Leu Phe Lys Arg Lys Glu
340 345 350

Ser Lys

<210> 9
<211> 1965
<212> DNA
<213> Staphylococcus epidermidis

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ttaatgtcaa atggcgaagc acaagcagca gctgaagaaa caggtggtac aaatacagaa 180

gcacaaccaa aaactgaagc agttgcaagt ccaacaacaa catctgaaaa agctccagaa 240

actaaaccag tagctaatgc tgtctcagta tctaataaag aagttgaggc ccctacttct 300

gaaacaaaag aagctaaaga agttaaagaa gttaaagccc ctaaggaaac aaaagaagtt 360

aaaccagcag caaaagccac taacaataca tatcctattt tgaatcagga acttagagaa 420

gcgattaaaa accctgcaat aaaagacaaa gatcatagcg caccaaactc tcgtccaatt 480

gattttgaaa tgaaaaagaa agatggaact caacagtttt atcattatgc aagttctgtt 540

aaacctgcta gagttatttt cactgattca aaaccagaaa ttgaattagg attacaatca 600

ggtcaatttt ggagaaaatt tgaagtttat gaaggtgaca aaaagttgcc aattaaatta 660

gtatcatacg atactgttaa agattatgct tacattcgct tctctgtatc aaacggaaca 720

aaagctgtta aaattgttag ttcaacacac ttcaataaca aagaagaaaa atacgattac 780

acattaatgg aattcgcaca accaatttat aacagtgcag ataaattcaa aactgaagaa 840

gattataaag ctgaaaaatt attagcgcca tataaaaaag cgaaaacact agaaagacaa 900

gtttatgaat taaataaaat tcaagataaa cttcctgaaa aattaaaggc tgagtacaag 960

aagaaattag aggatacaaa gaaagcttta gatgagcaag tgaaatcagc tattactgaa 1020

ttccaaaatg tacaaccaac aaatgaaaaa atgactgatt tacaagatac aaaatatgtt 1080

gtttatgaaa gtgttgagaa taacgaatct atgatggata cttttgttaa acaccctatt 1140

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gaagcattta caaaagccaa taccgataaa tctaacaaaa aagaacaaca agataactca 1440

gctaagaagg aagctactcc agctacgcct agcaaaccaa caccatcacc tgttgaaaaa 1500

gaatcacaaa aacaagacag ccaaaaagat gacaataaac aattaccaag tgttgaaaaa 1560

gaaaatgacg catctagtga gtcaggtaaa gacaaaacgc ctgctacaaa accaactaaa 1620

ggtgaagtag aatcaagtag tacaactcca actaaggtag tatctacgac tcaaaatgtt 1680

gcaaaaccaa caactgcttc atcaaaaaca acaaaagatg ttgttcaaac ttcagcaggt 1740

tctagcgaag caaaagatag tgctccatta caaaaagcaa acattaaaaa cacaaatgat 1800

ggacacactc aaagccaaaa caataaaaat acacaagaaa ataaagcaaa atcattacca 1860

caaactggtg aagaatcaaa taaagatatg acattaccat taatggcatt attagcttta 1920

agtagcatcg ttgcattcgt attacctaga aaacgtaaaa actaa 1965

<210> 10
<211> 654
<212> PRT
<213> Staphylococcus epidermidis

<400> 10

Tyr Thr Ile Arg Ser Cys Phe Tyr Asn Met Asn Lys Gln Gln Lys Glu
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Phe Lys Ser Phe Tyr Ser Ile Arg Lys Ser Ser Leu Gly Val Ala Ser
20 25 30

Val Ala Ile Ser Thr Leu Leu Leu Leu Met Ser Asn Gly Glu Ala Gln
35 40 45

Ala Ala Ala Glu Glu Thr Gly Gly Thr Asn Thr Glu Ala Gln Pro Lys
50 55 60

Thr Glu Ala Val Ala Ser Pro Thr Thr Thr Ser Glu Lys Ala Pro Glu
65 70 75 80

Thr Lys Pro Val Ala Asn Ala Val Ser Val Ser Asn Lys Glu Val Glu
85 90 95

Ala Pro Thr Ser Glu Thr Lys Glu Ala Lys Glu Val Lys Glu Val Lys
100 105 110

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Ala Pro Lys Glu Thr Lys Glu Val Lys Pro Ala Ala Lys Ala Thr Asn
        115                 120                 125

Asn Thr Tyr Pro Ile Leu Asn Gln Glu Leu Arg Glu Ala Ile Lys Asn
    130                 135                 140

Pro Ala Ile Lys Asp Lys Asp His Ser Ala Pro Asn Ser Arg Pro Ile
145                 150                 155                 160

Asp Phe Glu Met Lys Lys Lys Asp Gly Thr Gln Gln Phe Tyr His Tyr
                165                 170                 175

Ala Ser Ser Val Lys Pro Ala Arg Val Ile Phe Thr Asp Ser Lys Pro
            180                 185                 190

Glu Ile Glu Leu Gly Leu Gln Ser Gly Gln Phe Trp Arg Lys Phe Glu
        195                 200                 205

Val Tyr Glu Gly Asp Lys Lys Leu Pro Ile Lys Leu Val Ser Tyr Asp
    210                 215                 220

Thr Val Lys Asp Tyr Ala Tyr Ile Arg Phe Ser Val Ser Asn Gly Thr
225                 230                 235                 240

Lys Ala Val Lys Ile Val Ser Ser Thr His Phe Asn Asn Lys Glu Glu
                245                 250                 255

Lys Tyr Asp Tyr Thr Leu Met Glu Phe Ala Gln Pro Ile Tyr Asn Ser
            260                 265                 270

Ala Asp Lys Phe Lys Thr Glu Glu Asp Tyr Lys Ala Glu Lys Leu Leu
        275                 280                 285

Ala Pro Tyr Lys Lys Ala Lys Thr Leu Glu Arg Gln Val Tyr Glu Leu
    290                 295                 300

Asn Lys Ile Gln Asp Lys Leu Pro Glu Lys Leu Lys Ala Glu Tyr Lys
305                 310                 315                 320

Lys Lys Leu Glu Asp Thr Lys Lys Ala Leu Asp Glu Gln Val Lys Ser
                325                 330                 335

Ala Ile Thr Glu Phe Gln Asn Val Gln Pro Thr Asn Glu Lys Met Thr
            340                 345                 350

Asp Leu Gln Asp Thr Lys Tyr Val Val Tyr Glu Ser Val Glu Asn Asn
        355                 360                 365

Glu Ser Met Met Asp Thr Phe Val Lys His Pro Ile Lys Thr Gly Met
    370                 375                 380

Leu Asn Gly Lys Lys Tyr Met Val Met Glu Thr Thr Asn Asp Asp Tyr
385                 390                 395                 400

Trp Lys Asp Phe Met Val Glu Gly Gln Arg Val Arg Thr Ile Ser Lys
                405                 410                 415

Asp Ala Lys Asn Asn Thr Arg Thr Ile Ile Phe Pro Tyr Val Glu Gly
            420                 425                 430
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Lys Thr Leu Tyr Asp Ala Ile Val Lys Val His Val Lys Thr Ile Asp
435 440 445

Tyr Asp Gly Gln Tyr His Val Arg Ile Val Asp Lys Glu Ala Phe Thr
450 455 460

Lys Ala Asn Thr Asp Lys Ser Asn Lys Lys Glu Gln Gln Asp Asn Ser
465 470 475 480

Ala Lys Lys Glu Ala Thr Pro Ala Thr Pro Ser Lys Pro Thr Pro Ser
485 490 495

Pro Val Glu Lys Glu Ser Gln Lys Gln Asp Ser Gln Lys Asp Asp Asn
500 505 510

Lys Gln Leu Pro Ser Val Glu Lys Glu Asn Asp Ala Ser Ser Glu Ser
515 520 525

Gly Lys Asp Lys Thr Pro Ala Thr Lys Pro Thr Lys Gly Glu Val Glu
530 535 540

Ser Ser Ser Thr Thr Pro Thr Lys Val Val Ser Thr Thr Gln Asn Val
545 550 555 560

Ala Lys Pro Thr Thr Ala Ser Ser Lys Thr Thr Lys Asp Val Val Gln
565 570 575

Thr Ser Ala Gly Ser Ser Glu Ala Lys Asp Ser Ala Pro Leu Gln Lys
580 585 590

Ala Asn Ile Lys Asn Thr Asn Asp Gly His Thr Gln Ser Gln Asn Asn
595 600 605

Lys Asn Thr Gln Glu Asn Lys Ala Lys Ser Leu Pro Gln Thr Gly Glu
610 615 620

Glu Ser Asn Lys Asp Met Thr Leu Pro Leu Met Ala Leu Leu Ala Leu
625 630 635 640

Ser Ser Ile Val Ala Phe Val Leu Pro Arg Lys Arg Lys Asn
645 650

<210> 11
<211> 2406
<212> DNA
<213> Staphylococcus epidermidis

<400> 11
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ctcgttttgc tttttagtgt aatgggatta tggcaagtct cgaacgcggc tgagcagcat 180

acaccaatga aagcacatgc agtaacaacg atagacaaag caacaacaga taagcaacaa 240

gtaccgccaa caaaggaagc ggctcatcat tctggcaaag aagcggcaac caacgtatca 300

gcatcagcgc agggaacagc tgatgataca aacagcaaag taacatccaa cgcaccatct 360

aacaaaccat ctacagtagt ttcaacaaaa gtaaacgaaa cacgcgacgt agatacacaa 420

caagcctcaa cacaaaaacc aactcacaca gcaacgttca aattatcaaa tgctaaaaca 480

gcatcacttt caccacgaat gtttgctgct aatgcaccac aaacaacaac acataaaata 540

ttacatacaa atgatatcca tggccgacta gccgaagaaa aagggcgtgt catcggtatg 600

gctaaattaa aaacagtaaa agaacaagaa aagcctgatt taatgttaga cgcaggagac 660

gccttccaag gtttaccact ttcaaaccag tctaaaggtg aagaaatggc taaagcaatg 720

aatgcagtag gttatgatgc tatggcagtc ggtaaccatg aatttgactt tggatacgat 780

cagttgaaaa agttagaggg tatgttagac ttcccgatgc taagtactaa cgtttataaa 840

gatggaaaac gcgcgtttaa gccttcaacg attgtaacaa aaaatggtat tcgttatgga 900

attattggtg taacgacacc agaaacaaag acgaaaacaa gacctgaagg cattaaaggc 960

gttgaattta gagatccatt acaaagtgtg acagcggaaa tgatgcgtat ttataaagac 1020

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cgtggtgatt acttagtgaa acaattaagt caaaatccac aattgaagaa acgtattaca 1140

gttattgatg gtcattcaca tacagtactt caaaatggtc aaatttataa caatgatgca 1200

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gcagaggtaa ttattccaaa caataccatt gatttcaaag gagaaagaga tgacgttaga 1440

acgcgtgaaa caaatttagg aaacgcgatt gcagatgcta tggaagcgta tggcgttaag 1500

aatttctcta aaaagactga ctttgccgtg acaaatggtg gaggtattcg tgcctctatc 1560

gcaaaaggta aggtgacacg ctatgattta atctcagtat taccatttgg aaatacgatt 1620

gcgcaaattg atgtaaaagg ttcagacgtc tggacggctt tcgaacatag tttaggcgca 1680

ccaacaacac aaaaggacgg taagacagtg ttaacagcga atggcggttt actacatatc 1740

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attcaaattt taaataaaga gacaggtaag tttgaaaata ttgatttaaa acgtgtatat 1860

cacgtaacga tgaatgactt cacagcatca ggtggcgacg gatatagtat gttcggtggt 1920

cctagagaag aaggtatttc attagatcaa gtactagcaa gttatttaaa aacagctaac 1980

ttagctaagt atgatacgac agaaccacaa cgtatgttat taggtaaacc agcagtaagt 2040

gaacaaccag ctaaaggaca acaaggtagc aaaggtagta agtctggtaa agatacacaa 2100

ccaattggtg acgacaaagt gatggatcca gcgaaaaaac cagctccagg taaagttgta 2160

ttgttgctag cgcatagagg aactgttagt agcggtacag aaggttctgg tcgcacaata 2220

gaaggagcta ctgtatcaag caagagtggg aaacaattgg ctagaatgtc agtgcctaaa 2280

ggtagcgcgc atgagaaaca gttaccaaaa actggaacta atcaaagttc aagcccagaa 2340

gcgatgtttg tattattagc aggtataggt ttaatcgcga ctgtacgacg tagaaaagct 2400

agctaa 2406

<210> 12
<211> 801
<212> PRT
<213> Staphylococcus epidermidis

<400> 12

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Ile Ile Tyr Trp Cys Met Thr Val Asn Gly Gly Asn Glu Met Lys Ala
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Leu Leu Leu Lys Thr Ser Val Trp Leu Val Leu Leu Phe Ser Val Met
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Gly Leu Trp Gln Val Ser Asn Ala Ala Glu Gln His Thr Pro Met Lys
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Ala His Ala Val Thr Thr Ile Asp Lys Ala Thr Thr Asp Lys Gln Gln
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Val Pro Pro Thr Lys Glu Ala Ala His His Ser Gly Lys Glu Ala Ala
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Thr Asn Val Ser Ala Ser Ala Gln Gly Thr Ala Asp Asp Thr Asn Ser
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Lys Val Thr Ser Asn Ala Pro Ser Asn Lys Pro Ser Thr Val Val Ser
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Thr Lys Val Asn Glu Thr Arg Asp Val Asp Thr Gln Gln Ala Ser Thr
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Gln Lys Pro Thr His Thr Ala Thr Phe Lys Leu Ser Asn Ala Lys Thr
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Ala Ser Leu Ser Pro Arg Met Phe Ala Ala Asn Ala Pro Gln Thr Thr
165 170 175

Thr His Lys Ile Leu His Thr Asn Asp Ile His Gly Arg Leu Ala Glu
180 185 190

Glu Lys Gly Arg Val Ile Gly Met Ala Lys Leu Lys Thr Val Lys Glu
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Gln Glu Lys Pro Asp Leu Met Leu Asp Ala Gly Asp Ala Phe Gln Gly
210 215 220

Leu Pro Leu Ser Asn Gln Ser Lys Gly Glu Glu Met Ala Lys Ala Met

225 230 235 240

Asn Ala Val Gly Tyr Asp Ala Met Ala Val Gly Asn His Glu Phe Asp
245 250 255

Phe Gly Tyr Asp Gln Leu Lys Lys Leu Glu Gly Met Leu Asp Phe Pro
260 265 270

Met Leu Ser Thr Asn Val Tyr Lys Asp Gly Lys Arg Ala Phe Lys Pro
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Ser Thr Ile Val Thr Lys Asn Gly Ile Arg Tyr Gly Ile Ile Gly Val
290 295 300

Thr Thr Pro Glu Thr Lys Thr Lys Thr Arg Pro Glu Gly Ile Lys Gly
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Val Glu Phe Arg Asp Pro Leu Gln Ser Val Thr Ala Glu Met Met Arg
325 330 335

Ile Tyr Lys Asp Val Asp Thr Phe Val Val Ile Ser His Leu Gly Ile
340 345 350

Asp Pro Ser Thr Gln Glu Thr Trp Arg Gly Asp Tyr Leu Val Lys Gln
355 360 365

Leu Ser Gln Asn Pro Gln Leu Lys Lys Arg Ile Thr Val Ile Asp Gly
370 375 380

His Ser His Thr Val Leu Gln Asn Gly Gln Ile Tyr Asn Asn Asp Ala
385 390 395 400

Leu Ala Gln Thr Gly Thr Ala Leu Ala Asn Ile Gly Lys Ile Thr Phe
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Asn Tyr Arg Asn Gly Glu Val Ser Asn Ile Lys Pro Ser Leu Ile Asn
420 425 430

Val Lys Asp Val Glu Asn Val Thr Pro Asn Lys Ala Leu Ala Glu Gln
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Ile Asn Gln Ala Asp Gln Thr Phe Arg Ala Gln Thr Ala Glu Val Ile
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Ile Pro Asn Asn Thr Ile Asp Phe Lys Gly Glu Arg Asp Asp Val Arg
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Thr Arg Glu Thr Asn Leu Gly Asn Ala Ile Ala Asp Ala Met Glu Ala
485 490 495

Tyr Gly Val Lys Asn Phe Ser Lys Lys Thr Asp Phe Ala Val Thr Asn
500 505 510

Gly Gly Gly Ile Arg Ala Ser Ile Ala Lys Gly Lys Val Thr Arg Tyr
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Asp Leu Ile Ser Val Leu Pro Phe Gly Asn Thr Ile Ala Gln Ile Asp
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Val Lys Gly Ser Asp Val Trp Thr Ala Phe Glu His Ser Leu Gly Ala

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Pro Thr Thr Gln Lys Asp Gly Lys Thr Val Leu Thr Ala Asn Gly Gly
565 570 575

Leu Leu His Ile Ser Asp Ser Ile Arg Val Tyr Tyr Asp Ile Asn Lys
580 585 590

Pro Ser Gly Lys Arg Ile Asn Ala Ile Gln Ile Leu Asn Lys Glu Thr
595 600 605

Gly Lys Phe Glu Asn Ile Asp Leu Lys Arg Val Tyr His Val Thr Met
610 615 620

Asn Asp Phe Thr Ala Ser Gly Gly Asp Gly Tyr Ser Met Phe Gly Gly
625 630 635 640

Pro Arg Glu Glu Gly Ile Ser Leu Asp Gln Val Leu Ala Ser Tyr Leu
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Lys Thr Ala Asn Leu Ala Lys Tyr Asp Thr Thr Glu Pro Gln Arg Met
660 665 670

Leu Leu Gly Lys Pro Ala Val Ser Glu Gln Pro Ala Lys Gly Gln Gln
675 680 685

Gly Ser Lys Gly Ser Lys Ser Gly Lys Asp Thr Gln Pro Ile Gly Asp
690 695 700

Asp Lys Val Met Asp Pro Ala Lys Lys Pro Ala Pro Gly Lys Val Val
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Leu Leu Leu Ala His Arg Gly Thr Val Ser Ser Gly Thr Glu Gly Ser
725 730 735

Gly Arg Thr Ile Glu Gly Ala Thr Val Ser Ser Lys Ser Gly Lys Gln
740 745 750

Leu Ala Arg Met Ser Val Pro Lys Gly Ser Ala His Glu Lys Gln Leu
755 760 765

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gctgaaaaca atattgagaa tccaactaca ttaaaagata atgtccaatc aaaagaagtg 240

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Leu Met Tyr Leu Gly Thr Gln Gln Glu Ala Glu Ala Ala Glu Asn Asn
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Ile Glu Asn Pro Thr Thr Leu Lys Asp Asn Val Gln Ser Lys Glu Val
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Ala Glu Thr Pro Lys Val Arg Lys Ala Arg Ser Val Asp Glu Gly Ser
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Phe Asp Ile Thr Arg Asp Ser Lys Asn Val Val Glu Ser Thr Pro Ile
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Thr Ile Gln Gly Lys Glu His Phe Glu Gly Tyr Gly Ser Val Asp Ile
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Gln Lys Lys Pro Thr Asp Leu Gly Val Ser Glu Val Thr Arg Phe Asn
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Val Gly Asn Glu Ser Asn Gly Leu Ile Gly Ala Leu Gln Leu Lys Asn
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Lys Ile Asp Phe Ser Lys Asp Phe Asn Phe Lys Val Arg Val Ala Asn
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Asn His Gln Ser Asn Thr Thr Gly Ala Asp Gly Trp Gly Phe Leu Phe
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Ser Lys Gly Asn Ala Glu Glu Tyr Leu Thr Asn Gly Gly Ile Leu Gly
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Asp Lys Gly Leu Val Asn Ser Gly Gly Phe Lys Ile Asp Thr Gly Tyr
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Tyr Arg Gly Tyr Gly Ala Phe Val Lys Asn Asp Ser Ser Gly Asn Ser
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Gln Met Val Gly Glu Asn Ile Asp Lys Ser Lys Thr Asn Phe Leu Asn
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Tyr Ala Asp Asn Ser Thr Asn Thr Ser Asp Gly Lys Phe His Gly Gln
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Arg Leu Asn Asp Val Ile Leu Thr Tyr Val Ala Ser Thr Gly Lys Met
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Arg Ala Glu Tyr Ala Gly Lys Thr Trp Glu Thr Ser Ile Thr Asp Leu
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Gly Leu Ser Lys Asn Gln Ala Tyr Asn Phe Leu Ile Thr Ser Ser Gln
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Asp Leu Lys Gly Ser Glu Phe Thr Phe Thr Pro Glu Ala Pro Lys Thr
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Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
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Pro Leu Thr Gly Val Ile Ile Ser Lys Gly Glu Pro Lys Glu Glu Ile
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Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr Ile
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Ala Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
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Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
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Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
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Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
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Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Glu Lys Glu
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Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
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Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
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Pro Leu Thr Gly Val Ile Ile Ser Lys Gly Glu Pro Lys Glu Glu Ile
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Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
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Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
785 790 795 800

Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
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Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Lys Lys Glu
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Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
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Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
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Pro Leu Thr Gly Glu Ile Ile Ser Lys Gly Glu Ser Lys Glu Glu Ile
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Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
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Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
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Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
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Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
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Ser Lys Gly Glu Ser Lys Glu Glu Ile Thr Lys Asp Pro Val Asn
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caaggatcag atttattaga cagtattcca gatataccca caccaaagcc agaaaagacg 1740

ttaacacttg gtaaaggtaa tggattgtta agtggattat taaatgctga tggtaatgta 1800

tctttgccta aagcggggga aacgataaaa gaacattggt tgccgatatc tgtaattgtt 1860

ggtgcaatgg gtgtactaat gatttggtta tcacgacgca ataagttgaa aaataaagca 1920

taa 1923

<210> 16
<211> 640
<212> PRT
<213> Staphylococcus epidermidis

<400> 16

Gly Arg Ser Met Leu Met Ala Lys Tyr Arg Gly Lys Pro Phe Gln Leu
1 5 10 15

Tyr Val Lys Leu Ser Cys Ser Thr Met Met Ala Thr Ser Ile Ile Leu
20 25 30

Thr Asn Ile Leu Pro Tyr Asp Ala Gln Ala Ala Ser Glu Lys Asp Thr
35 40 45

Glu Ile Thr Lys Glu Ile Leu Ser Lys Gln Asp Leu Leu Asp Lys Val
50 55 60

Asp Lys Ala Ile Arg Gln Ile Glu Gln Leu Lys Gln Leu Ser Ala Ser
65 70 75 80

Ser Lys Glu His Tyr Lys Ala Gln Leu Asn Glu Ala Lys Thr Ala Ser
85 90 95

Gln Ile Asp Glu Ile Ile Lys Arg Ala Asn Glu Leu Asp Ser Lys Asp
100 105 110

Asn Lys Ser Ser His Thr Glu Met Asn Gly Gln Ser Asp Ile Asp Ser
115 120 125

Lys Leu Asp Gln Leu Leu Lys Asp Leu Asn Glu Val Ser Ser Asn Val
130 135 140

Asp Arg Gly Gln Gln Ser Gly Glu Asp Asp Leu Asn Ala Met Lys Asn
145 150 155 160

Asp Met Ser Gln Thr Ala Thr Thr Lys His Gly Glu Lys Asp Asp Lys
165 170 175

Asn Asp Glu Ala Met Val Asn Lys Ala Leu Glu Asp Leu Asp His Leu
180 185 190

Asn Gln Gln Ile His Lys Ser Lys Asp Ala Ser Lys Asp Thr Ser Glu
195 200 205

Asp Pro Ala Val Ser Thr Thr Asp Asn Asn His Glu Val Ala Lys Thr

210 215 220

Pro Asn Asn Asp Gly Ser Gly His Val Val Leu Asn Lys Phe Leu Ser
225 230 235 240

Asn Glu Glu Asn Gln Ser His Ser Asn Arg Leu Thr Asp Lys Leu Gln
245 250 255

Gly Ser Asp Lys Ile Asn His Ala Met Ile Glu Lys Leu Ala Lys Ser
260 265 270

Asn Ala Ser Thr Gln His Tyr Thr Tyr His Lys Leu Asn Thr Leu Gln
275 280 285

Ser Leu Asp Gln Arg Ile Ala Asn Thr Gln Leu Pro Lys Asn Gln Lys
290 295 300

Ser Asp Leu Met Ser Glu Val Asn Lys Thr Lys Glu Arg Ile Lys Ser
305 310 315 320

Gln Arg Asn Ile Ile Leu Glu Glu Leu Ala Arg Thr Asp Asp Lys Lys
325 330 335

Tyr Ala Thr Gln Ser Ile Leu Glu Ser Ile Phe Asn Lys Asp Glu Ala
340 345 350

Val Lys Ile Leu Lys Asp Ile Arg Val Asp Gly Lys Thr Asp Gln Gln
355 360 365

Ile Ala Asp Gln Ile Thr Arg His Ile Asp Gln Leu Ser Leu Thr Thr
370 375 380

Ser Asp Asp Leu Leu Thr Ser Leu Ile Asp Gln Ser Gln Asp Lys Ser
385 390 395 400

Leu Leu Ile Ser Gln Ile Leu Gln Thr Lys Leu Gly Lys Ala Glu Ala
405 410 415

Asp Lys Leu Ala Lys Asp Trp Thr Asn Lys Gly Leu Ser Asn Arg Gln
420 425 430

Ile Val Asp Gln Leu Lys Lys His Phe Ala Ser Thr Gly Asp Thr Ser
435 440 445

Ser Asp Asp Ile Leu Lys Ala Ile Leu Asn Asn Ala Lys Asp Lys Lys
450 455 460

Gln Ala Ile Glu Thr Ile Leu Ala Thr Arg Ile Glu Arg Gln Lys Ala
465 470 475 480

Lys Leu Leu Ala Asp Leu Ile Thr Lys Ile Glu Thr Asp Gln Asn Lys
485 490 495

Ile Phe Asn Leu Val Lys Ser Ala Leu Asn Gly Lys Ala Asp Asp Leu
500 505 510

Leu Asn Leu Gln Lys Arg Leu Asn Gln Thr Lys Lys Asp Ile Asp Tyr
515 520 525

Ile Leu Ser Pro Ile Val Asn Arg Pro Ser Leu Leu Asp Arg Leu Asn

530 535 540

Lys Asn Gly Lys Thr Thr Asp Leu Asn Lys Leu Ala Asn Leu Met Asn
545 550 555 560

Gln Gly Ser Asp Leu Leu Asp Ser Ile Pro Asp Ile Pro Thr Pro Lys
565 570 575

Pro Glu Lys Thr Leu Thr Leu Gly Lys Gly Asn Gly Leu Leu Ser Gly
580 585 590

Leu Leu Asn Ala Asp Gly Asn Val Ser Leu Pro Lys Ala Gly Glu Thr
595 600 605

Ile Lys Glu His Trp Leu Pro Ile Ser Val Ile Val Gly Ala Met Gly
610 615 620

Val Leu Met Ile Trp Leu Ser Arg Arg Asn Lys Leu Lys Asn Lys Ala
625 630 635 640

<210> 17
<211> 522
<212> PRT
<213> Staphylococcus epidermidis

<400> 17

Ala Ser Glu Thr Pro Ile Thr Ser Glu Ile Ser Ser Asn Ser Glu Thr
1 5 10 15

Val Ala Asn Gln Asn Ser Thr Thr Ile Lys Asn Ser Gln Lys Glu Thr
20 25 30

Val Asn Ser Thr Ser Leu Glu Ser Asn His Ser Asn Ser Thr Asn Lys
35 40 45

Gln Met Ser Ser Glu Val Thr Asn Thr Ala Gln Ser Ser Glu Lys Ala
50 55 60

Gly Ile Ser Gln Gln Ser Ser Glu Thr Ser Asn Gln Ser Ser Lys Leu
65 70 75 80

Asn Thr Tyr Ala Ser Thr Asp His Val Glu Ser Thr Thr Ile Asn Asn
85 90 95

Asp Asn Thr Ala Gln Gln Asp Gln Asn Lys Ser Ser Asn Val Thr Ser
100 105 110

Lys Ser Thr Gln Ser Asn Thr Ser Ser Ser Glu Lys Asn Ile Ser Ser
115 120 125

Asn Leu Thr Gln Ser Ile Glu Thr Lys Ala Thr Asp Ser Leu Ala Thr
130 135 140

Ser Glu Ala Arg Thr Ser Thr Asn Gln Ile Ser Asn Leu Thr Ser Thr
145 150 155 160

Ser Thr Ser Asn Gln Ser Ser Pro Thr Ser Phe Ala Asn Leu Arg Thr
165 170 175

Phe Ser Arg Phe Thr Val Leu Asn Thr Met Ala Ala Pro Thr Thr Thr
180 185 190

Ser Thr Thr Thr Thr Ser Ser Leu Thr Ser Asn Ser Val Val Val Asn
195 200 205

Lys Asp Asn Phe Asn Glu His Met Asn Leu Ser Gly Ser Ala Thr Tyr
210 215 220

Asp Pro Lys Thr Gly Ile Ala Thr Leu Thr Pro Asp Ala Tyr Ser Gln
225 230 235 240

Lys Gly Ala Ile Ser Leu Asn Thr Arg Leu Asp Ser Asn Arg Ser Phe
245 250 255

Arg Phe Ile Gly Lys Val Asn Leu Gly Asn Arg Tyr Glu Gly Tyr Ser
260 265 270

Pro Asp Gly Val Ala Gly Gly Asp Gly Ile Gly Phe Ala Phe Ser Pro
275 280 285

Gly Pro Leu Gly Gln Ile Gly Lys Glu Gly Ala Ala Val Gly Ile Gly
290 295 300

Gly Leu Asn Asn Ala Phe Gly Phe Lys Leu Asp Thr Tyr His Asn Thr
305 310 315 320

Ser Thr Pro Arg Ser Asp Ala Lys Ala Lys Ala Asp Pro Arg Asn Val
325 330 335

Gly Gly Gly Gly Ala Phe Gly Ala Phe Val Ser Thr Asp Arg Asn Gly
340 345 350

Met Ala Thr Thr Glu Glu Ser Thr Ala Ala Lys Leu Asn Val Gln Pro
355 360 365

Thr Asp Asn Ser Phe Gln Asp Phe Val Ile Asp Tyr Asn Gly Asp Thr
370 375 380

Lys Val Met Thr Val Thr Tyr Ala Gly Gln Thr Phe Thr Arg Asn Leu
385 390 395 400

Thr Asp Trp Ile Lys Asn Ser Gly Gly Thr Thr Phe Ser Leu Ser Met
405 410 415

Thr Ala Ser Thr Gly Gly Ala Lys Asn Leu Gln Gln Val Gln Phe Gly
420 425 430

Thr Phe Glu Tyr Thr Glu Ser Ala Val Ala Lys Val Arg Tyr Val Asp
435 440 445

Ala Asn Thr Gly Lys Asp Ile Ile Pro Pro Lys Thr Ile Ala Gly Glu
450 455 460

Val Asp Gly Thr Val Asn Ile Asp Lys Gln Leu Asn Asn Phe Lys Asn
465 470 475 480

Leu Gly Tyr Ser Tyr Val Gly Thr Asp Ala Leu Lys Ala Pro Asn Tyr
485 490 495

Thr Glu Thr Ser Gly Thr Pro Thr Leu Lys Leu Thr Asn Ser Ser Gln
500 505 510

Thr Val Ile Tyr Lys Phe Lys Asp Val Gln
515 520

<210> 18
<211> 485
<212> PRT
<213> Staphylococcus epidermidis

<400> 18

Ala Ser Asp Ala Pro Leu Thr Ser Glu Leu Asn Thr Gln Ser Glu Thr
1 5 10 15

Val Gly Asn Gln Asn Ser Thr Thr Ile Glu Ala Ser Thr Ser Thr Ala
20 25 30

Asp Ser Thr Ser Val Thr Lys Asn Ser Ser Ser Val Gln Thr Ser Asn
35 40 45

Ser Asp Thr Val Ser Ser Glu Lys Ser Glu Lys Val Thr Ser Thr Thr
50 55 60

Asn Ser Thr Ser Asn Gln Gln Glu Lys Leu Thr Ser Thr Ser Glu Ser
65 70 75 80

Thr Ser Ser Lys Asn Thr Thr Ser Ser Ser Asp Thr Lys Ser Val Ala
85 90 95

Ser Thr Ser Ser Thr Glu Gln Pro Ile Asn Thr Ser Thr Asn Gln Ser
100 105 110

Thr Ala Ser Asn Asn Thr Ser Gln Ser Thr Thr Pro Ser Ser Val Asn
115 120 125

Leu Asn Lys Thr Ser Thr Thr Ser Thr Ser Thr Ala Pro Val Lys Leu
130 135 140

Arg Thr Phe Ser Arg Leu Ala Met Ser Thr Phe Ala Ser Ala Ala Thr
145 150 155 160

Thr Thr Ala Val Thr Ala Asn Thr Ile Thr Val Asn Lys Asp Asn Leu
165 170 175

Lys Gln Tyr Met Thr Thr Ser Gly Asn Ala Thr Tyr Asp Gln Ser Thr
180 185 190

Gly Ile Val Thr Leu Thr Gln Asp Ala Tyr Ser Gln Lys Gly Ala Ile
195 200 205

Thr Leu Gly Thr Arg Ile Asp Ser Asn Lys Ser Phe His Phe Ser Gly
210 215 220

Lys Val Asn Leu Gly Asn Lys Tyr Glu Gly His Gly Asn Gly Gly Asp
225 230 235 240

Gly Ile Gly Phe Ala Phe Ser Pro Gly Val Leu Gly Glu Thr Gly Leu
245 250 255

Asn Gly Ala Ala Val Gly Ile Gly Gly Leu Ser Asn Ala Phe Gly Phe
260 265 270

Lys Leu Asp Thr Tyr His Asn Thr Ser Lys Pro Asn Ser Ala Ala Lys
275 280 285

Ala Asn Ala Asp Pro Ser Asn Val Ala Gly Gly Gly Ala Phe Gly Ala
290 295 300

Phe Val Thr Thr Asp Ser Tyr Gly Val Ala Thr Thr Tyr Thr Ser Ser
305 310 315 320

Ser Thr Ala Asp Asn Ala Ala Lys Leu Asn Val Gln Pro Thr Asn Asn
325 330 335

Thr Phe Gln Asp Phe Asp Ile Asn Tyr Asn Gly Asp Thr Lys Val Met
340 345 350

Thr Val Lys Tyr Ala Gly Gln Thr Trp Thr Arg Asn Ile Ser Asp Trp
355 360 365

Ile Ala Lys Ser Gly Thr Thr Asn Phe Ser Leu Ser Met Thr Ala Ser
370 375 380

Thr Gly Gly Ala Thr Asn Leu Gln Gln Val Gln Phe Gly Thr Phe Glu
385 390 395 400

Tyr Thr Glu Ser Ala Val Thr Gln Val Arg Tyr Val Asp Val Thr Thr
405 410 415

Gly Lys Asp Ile Ile Pro Pro Lys Thr Tyr Ser Gly Asn Val Asp Gln
420 425 430

Val Val Thr Ile Asp Asn Gln Gln Ser Ala Leu Thr Ala Lys Gly Tyr
435 440 445

Asn Tyr Thr Ser Val Asp Ser Ser Tyr Ala Ser Thr Tyr Asn Asp Thr
450 455 460

Asn Lys Thr Val Lys Met Thr Asn Ala Gly Gln Ser Val Thr Tyr Tyr
465 470 475 480

Phe Thr Asp Val Val
485

<210> 19
<211> 1245
<212> PRT
<213> Staphylococcus epidermidis

<400> 19

Met Gly Lys Arg Arg Gln Gly Pro Ile Asn Lys Lys Val Asp Phe Leu
1 5 10 15

Pro Asn Lys Leu Asn Lys Tyr Ser Ile Arg Lys Phe Thr Val Gly Thr
20 25 30

Ala Ser Ile Leu Leu Gly Ser Thr Leu Ile Phe Gly Ser Ser Ser His

35 40 45

Glu Ala Lys Ala Ala Glu Glu Lys Gln Val Asp Pro Ile Thr Gln Ala
50 55 60

Asn Gln Asn Asp Ser Ser Glu Arg Ser Leu Glu Asn Thr Asn Gln Pro
65 70 75 80

Thr Val Asn Asn Glu Ala Pro Gln Met Ser Ser Thr Leu Gln Ala Glu
85 90 95

Glu Gly Ser Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu
100 105 110

Glu Gly Gly Asn Ala Glu Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu
115 120 125

Glu Gly Gly Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu
130 135 140

Glu Gly Gly Asn Ala Glu Ala Ala Gln Ser Glu Pro Thr Lys Thr Glu
145 150 155 160

Glu Gly Ser Asn Val Lys Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu
165 170 175

Glu Gly Ser Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu
180 185 190

Glu Gly Ser Asn Ala Lys Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu
195 200 205

Glu Gly Gly Asn Ala Glu Ala Ala Gln Ser Glu Pro Thr Lys Thr Glu
210 215 220

Glu Gly Ser Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu
225 230 235 240

Glu Gly Gly Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu
245 250 255

Glu Gly Gly Asn Ala Glu Ala Pro Asn Val Pro Thr Ile Lys Ala Asn
260 265 270

Ser Asp Asn Asp Thr Gln Thr Gln Phe Ser Glu Ala Pro Thr Arg Asn
275 280 285

Asp Leu Ala Arg Lys Glu Asp Ile Pro Ala Val Ser Lys Asn Glu Glu
290 295 300

Leu Gln Ser Ser Gln Pro Asn Thr Asp Ser Lys Ile Glu Pro Thr Thr
305 310 315 320

Ser Glu Pro Val Asn Leu Asn Tyr Ser Ser Pro Phe Met Ser Leu Leu
325 330 335

Ser Met Pro Ala Asp Ser Ser Ser Asn Asn Thr Lys Asn Thr Ile Asp
340 345 350

Ile Pro Pro Thr Thr Val Lys Gly Arg Asp Asn Tyr Asp Phe Tyr Gly

355 360 365

Arg Val Asp Ile Glu Ser Asn Pro Thr Asp Leu Asn Ala Thr Asn Leu
370 375 380

Thr Arg Tyr Asn Tyr Gly Gln Pro Pro Gly Thr Thr Thr Ala Gly Ala
385 390 395 400

Val Gln Phe Lys Asn Gln Val Ser Phe Asp Lys Asp Phe Asp Phe Asn
405 410 415

Ile Arg Val Ala Asn Asn Arg Gln Ser Asn Thr Thr Gly Ala Asp Gly
420 425 430

Trp Gly Phe Met Phe Ser Lys Lys Asp Gly Asp Asp Phe Leu Lys Asn
435 440 445

Gly Gly Ile Leu Arg Glu Lys Gly Thr Pro Ser Ala Ala Gly Phe Arg
450 455 460

Ile Asp Thr Gly Tyr Tyr Asn Asn Asp Pro Leu Asp Lys Ile Gln Lys
465 470 475 480

Gln Ala Gly Gln Gly Tyr Arg Gly Tyr Gly Thr Phe Val Lys Asn Asp
485 490 495

Ser Gln Gly Asn Thr Ser Lys Val Gly Ser Gly Thr Pro Ser Thr Asp
500 505 510

Phe Leu Asn Tyr Ala Asp Asn Thr Thr Asn Asp Leu Asp Gly Lys Phe
515 520 525

His Gly Gln Lys Leu Asn Asn Val Asn Leu Lys Tyr Asn Ala Ser Asn
530 535 540

Gln Thr Phe Thr Ala Thr Tyr Ala Gly Lys Thr Trp Thr Ala Thr Leu
545 550 555 560

Ser Glu Leu Gly Leu Ser Pro Thr Asp Ser Tyr Asn Phe Leu Val Thr
565 570 575

Ser Ser Gln Tyr Gly Asn Gly Asn Ser Gly Thr Tyr Ala Ser Gly Val
580 585 590

Met Arg Ala Asp Leu Asp Gly Ala Thr Leu Thr Tyr Thr Pro Lys Ala
595 600 605

Val Asp Gly Asp Pro Ile Ile Ser Thr Lys Glu Ile Pro Phe Asn Lys
610 615 620

Lys Arg Glu Phe Asp Pro Asn Leu Ala Pro Gly Thr Glu Lys Val Val
625 630 635 640

Gln Lys Gly Glu Pro Gly Ile Glu Thr Thr Thr Thr Pro Thr Tyr Val
645 650 655

Asn Pro Asn Thr Gly Glu Lys Val Gly Glu Gly Glu Pro Thr Glu Lys
660 665 670

Ile Thr Lys Gln Pro Val Asp Glu Ile Val His Tyr Gly Gly Glu Glu

675 680 685

Ile Lys Pro Gly His Lys Asp Glu Phe Asp Pro Asn Ala Pro Lys Gly
690 695 700

Ser Gln Thr Thr Gln Pro Gly Lys Pro Gly Val Lys Asn Pro Asp Thr
705 710 715 720

Gly Glu Val Val Thr Pro Pro Val Asp Asp Val Thr Lys Tyr Gly Pro
725 730 735

Val Asp Gly Asp Pro Ile Thr Ser Thr Glu Glu Ile Pro Phe Asp Lys
740 745 750

Lys Arg Glu Phe Asn Pro Asp Leu Lys Pro Gly Glu Glu Arg Val Lys
755 760 765

Gln Lys Gly Glu Pro Gly Thr Lys Thr Ile Thr Thr Pro Thr Thr Lys
770 775 780

Asn Pro Leu Thr Gly Glu Lys Val Gly Glu Gly Glu Pro Thr Glu Lys
785 790 795 800

Ile Thr Lys Gln Pro Val Asp Glu Ile Thr Glu Tyr Gly Gly Glu Glu
805 810 815

Ile Lys Pro Gly His Lys Asp Glu Phe Asp Pro Asn Ala Pro Lys Gly
820 825 830

Ser Gln Glu Asp Val Pro Gly Lys Pro Gly Val Lys Asn Pro Gly Thr
835 840 845

Gly Glu Val Val Thr Pro Pro Val Asp Asp Val Thr Lys Tyr Gly Pro
850 855 860

Val Asp Gly Asp Pro Ile Thr Ser Thr Glu Glu Ile Pro Phe Asp Lys
865 870 875 880

Lys Arg Glu Phe Asn Pro Asp Leu Lys Pro Gly Glu Glu Arg Val Lys
885 890 895

Gln Lys Gly Glu Pro Gly Thr Lys Thr Ile Thr Thr Pro Thr Thr Lys
900 905 910

Asn Pro Leu Thr Gly Glu Lys Val Gly Glu Gly Glu Pro Thr Glu Lys
915 920 925

Ile Thr Lys Gln Pro Val Asp Glu Ile Val His Tyr Gly Gly Glu Gln
930 935 940

Ile Pro Gln Gly His Lys Asp Glu Phe Asp Pro Asn Ala Pro Val Asp
945 950 955 960

Ser Lys Thr Glu Val Pro Gly Lys Pro Gly Val Lys Asn Pro Asp Thr
965 970 975

Gly Glu Val Val Thr Pro Pro Val Asp Asp Val Thr Lys Tyr Gly Pro
980 985 990

Val Asp Gly Asp Ser Ile Thr Ser Thr Glu Glu Ile Pro Phe Asp Lys

995 1000 1005

Lys Arg Glu Phe Asp Pro Asn Leu Ala Pro Gly Thr Glu Lys Val
1010 1015 1020

Val Gln Lys Gly Glu Pro Gly Thr Lys Thr Ile Thr Thr Pro Thr
1025 1030 1035

Thr Lys Asn Pro Leu Thr Gly Glu Lys Val Gly Glu Gly Lys Ser
1040 1045 1050

Thr Glu Lys Val Thr Lys Gln Pro Val Asp Glu Ile Val Glu Tyr
1055 1060 1065

Gly Pro Thr Lys Ala Glu Pro Gly Lys Pro Ala Glu Pro Gly Lys
1070 1075 1080

Pro Ala Glu Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu
1085 1090 1095

Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu Pro Gly Lys
1100 1105 1110

Pro Ala Glu Pro Gly Lys Pro Ala Glu Pro Gly Lys Pro Ala Glu
1115 1120 1125

Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu Pro Gly Thr
1130 1135 1140

Pro Ala Glu Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu
1145 1150 1155

Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu Pro Gly Lys
1160 1165 1170

Pro Ala Glu Ser Gly Lys Pro Val Glu Pro Gly Thr Pro Ala Gln
1175 1180 1185

Ser Gly Ala Pro Glu Gln Pro Asn Arg Ser Met His Ser Thr Asp
1190 1195 1200

Asn Lys Asn Gln Leu Pro Asp Thr Gly Glu Asn Arg Gln Ala Asn
1205 1210 1215

Glu Gly Thr Leu Val Gly Ser Leu Leu Ala Ile Val Gly Ser Leu
1220 1225 1230

Phe Ile Phe Gly Arg Arg Lys Lys Gly Asn Glu Lys
1235 1240 1245

<210> 20
<211> 3765
<212> DNA
<213> Staphylococcus epidermidis

<400> 20
atgggcaaac gtagacaagg tcctattaat aaaaaagtgg atttttacc taacaaatta 60

aacaagtatt ctataagaaa attcactgtt ggtacggcct caatattact tggttcgaca 120

cttatttttg gaagtagtag ccatgaagcg aaagctgcag aagaaaaaca agttgatcca 180

attacacaag ctaatcaaaa tgatagtagt gaaagatcac ttgaaaacac aaatcaacct 240

actgtaaaca atgaagcacc acagatgtct tctacattgc aagcagaaga aggaagcaat 300

gcagaagcac ctcaatctga gccaacgaag gcagaagaag gaggcaatgc agaagcagct 360

caatctgagc caacgaaggc agaagaagga ggcaatgcag aagcacctca atctgagcca 420

acgaaggcag aagaaggagg caatgcagaa gcagctcaat ctgagccaac gaagacagaa 480

gaaggaagca acgtaaaagc agctcaatct gagccaacga aggcagaaga aggaagcaat 540

gcagaagcac ctcaatctga gccaacgaag acagaagaag gaagcaacgc aaaagcagct 600

caatctgagc caacgaaggc agaagaagga ggcaatgcag aagcagctca atctgagcca 660

acgaagacag aagaaggaag caatgcagaa gcacctcaat ctgagccaac gaaggcagaa 720

gaaggaggca atgcagaagc acctcaatct gagccaacga agacagaaga aggaggcaat 780

gcagaagcac cgaatgttcc aactatcaaa gctaattcag ataatgatac acaaacacaa 840

ttttcagaag cccctacaag aaatgaccta gctagaaaag aagatatccc tgctgtttct 900

aaaaacgagg aattacaatc atcacaacca aacactgaca gtaaaataga acctacaact 960

tcagaacctg tgaatttaaa ttatagttct ccgtttatgt ccttattaag catgcctgct 1020

gatagttcat ccaataacac taaaaataca atagatatac cgccaactac ggttaaaggt 1080

agagataatt acgattttta cggtagagta gatatcgaaa gtaatcctac agatttaaat 1140

gcgacaaatt taacgagata taattatgga cagccacctg gtacaacaac agctggtgca 1200

gttcaattta aaaatcaagt tagttttgat aaagatttcg actttaacat tagagtagca 1260

aacaatcgtc aaagtaatac aactggtgca gatggttggg gctttatgtt cagcaagaaa 1320

gatggggatg atttcctaaa aaacggtggt atcttacgtg aaaaaggtac acctagtgca 1380

gctggtttca gaattgatac aggatattat aataacgatc cattagataa aatacagaaa 1440

caagctggtc aaggctatag agggtatggg acatttgtta aaaatgactc ccaaggtaat 1500

acttctaaag taggatcagg tactccatca acagattttc ttaactacgc agataatact 1560

actaatgatt tagatggtaa attccatggt caaaaattaa ataatgttaa tttgaaatat 1620

aatgcttcaa atcaaacttt tacagctact tatgctggta aaacttggac ggctacgtta 1680

tctgaattag gattgagtcc aactgatagt tacaattttt tagttacatc aagtcaatat 1740

ggaaatggta atagtggtac atacgcaagt ggcgttatga gagctgattt agatggtgca 1800

acattgacat acactcctaa agcagtcgat ggagatccaa ttatatcaac taaggaaata 1860

ccatttaata agaaacgtga atttgatcca aacttagccc caggtacaga aaaagtagtc 1920

caaaaaggtg aaccaggaat tgaaacaaca acaaccaccaa cttatgtcaa tcctaataca 1980

ggagaaaaag ttggcgaagg tgaaccaaca gaaaaaataa caaaacaacc agtggatgaa 2040

atcgttcatt atggtggcga agaaatcaag ccaggccata aggatgaatt tgatccaaat 2100

gcaccgaaag gtagtcaaac aacgcaacca ggtaagccgg gggttaaaaa tcctgataca 2160

ggcgaagtag ttactccacc tgtggatgat gtgacaaaat atggtccagt tgatggagat 2220

ccgatcacgt caacggaaga aattccattc gacaagaaac gtgaattcaa tcctgattta 2280

aaaccaggtg aagagcgtgt taaacaaaaa ggtgaaccag gaacaaaaac aattacaaca 2340

ccaacaacta agaacccatt aacaggggaa aaagttggcg aaggtgaacc aacagaaaaa 2400

ataacaaaac aaccagtaga tgaaatcaca gaatatggtg gcgaagaaat caagccaggc 2460

cataaggatg aatttgatcc aaatgcaccg aaaggtagcc aagaggacgt tccaggtaaa 2520

ccaggagtta aaaaccctgg aacaggcgaa gtagtcacac caccagtgga tgatgtgaca 2580

aaatatggtc cagttgatgg agatccgatc acgtcaacgg aagaaattcc attcgacaag 2640

aaacgtgaat tcaatcctga tttaaaacca ggtgaagagc gcgttaaaca gaaaggtgaa 2700

ccaggaacaa aaacaattac aacgccaaca actaagaacc cattaacagg agaaaaagtt 2760

ggcgaaggtg aaccaacaga aaaaataaca aaacaaccag tggatgagat tgttcattat 2820

ggtggtgaac aaataccaca aggtcataaa gatgaatttg atccaaatgc acctgtagat 2880

agtaaaactg aagttccagg taaaccagga gttaaaaatc ctgatacagg tgaagttgtt 2940

accccaccag tggatgatgt gacaaaatat ggtccagttg atggagattc gattacgtca 3000

acggaagaaa ttccgtttga taaaaaacgc gaatttgatc caaacttagc gccaggtaca 3060

gagaaagtcg ttcaaaaagg tgaaccagga acaaaaacaa ttacaacgcc aacaactaag 3120

aacccattaa caggagaaaa agttggcgaa ggtaaatcaa cagaaaaagt cactaaacaa 3180

cctgttgacg aaattgttga gtatggtcca acaaaagcag aaccaggtaa accagcggaa 3240

ccaggtaaac cagcggaacc aggtaaacca gcggaaccag gtacgccagc agaaccaggt 3300

aaaccagcgg aaccaggtac gccagcagaa ccaggtaaac cagcggaacc aggtaaacca 3360

gcggaaccag gtaaaccagc ggaaccaggt aaaccagcgg aaccaggtac gccagcagaa 3420

ccaggtacgc cagcagaacc aggtaaacca gcggaaccag gtacgccagc agaaccaggt 3480

aaaccagcgg aaccaggtac gccagcagaa ccaggtaaac cagcggaatc aggtaaacca 3540

gtggaaccag gtacgccagc acaatcaggt gcaccagaac aaccaaatag atcaatgcat 3600

tcaacagata ataaaaatca attacctgat acaggtgaaa atcgtcaagc taatgaggga 3660

actttagtcg gatctctatt agcaattgtc ggatcattgt tcatatttgg tcgtcgtaaa 3720

aaaggtaatg aaaaataatt tcatataaaa actttctgcc attaa 3765

<210> 21
<211> 546
<212> PRT
<213> Staphylococcus epidermidis

<400> 21

Glu Lys Gln Val Asp Pro Ile Thr Gln Ala Asn Gln Asn Asp Ser Ser
1 5 10 15

Glu Arg Ser Leu Glu Asn Thr Asn Gln Pro Thr Val Asn Asn Glu Ala
20 25 30

Pro Gln Met Ser Ser Thr Leu Gln Ala Glu Glu Gly Ser Asn Ala Glu
35 40 45

Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Gly Asn Ala Glu
50 55 60

Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Gly Asn Ala Glu
65 70 75 80

Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Gly Asn Ala Glu
85 90 95

Ala Ala Gln Ser Glu Pro Thr Lys Thr Glu Glu Gly Ser Asn Val Lys
100 105 110

Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Ser Asn Ala Glu
115 120 125

Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu Glu Gly Ser Asn Ala Lys
130 135 140

Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Gly Asn Ala Glu
145 150 155 160

Ala Ala Gln Ser Glu Pro Thr Lys Thr Glu Glu Gly Ser Asn Ala Glu
165 170 175

Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Gly Asn Ala Glu
180 185 190

Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu Glu Gly Gly Asn Ala Glu
195 200 205

Ala Pro Asn Val Pro Thr Ile Lys Ala Asn Ser Asp Asn Asp Thr Gln
210 215 220

Thr Gln Phe Ser Glu Ala Pro Thr Arg Asn Asp Leu Ala Arg Lys Glu
225 230 235 240

Asp Ile Pro Ala Val Ser Lys Asn Glu Glu Leu Gln Ser Ser Gln Pro
245 250 255

Asn Thr Asp Ser Lys Ile Glu Pro Thr Thr Ser Glu Pro Val Asn Leu
260 265 270

Asn Tyr Ser Ser Pro Phe Met Ser Leu Leu Ser Met Pro Ala Asp Ser
275 280 285

Ser Ser Asn Asn Thr Lys Asn Thr Ile Asp Ile Pro Pro Thr Thr Val
290 295 300

Lys Gly Arg Asp Asn Tyr Asp Phe Tyr Gly Arg Val Asp Ile Glu Ser
305 310 315 320

Asn Pro Thr Asp Leu Asn Ala Thr Asn Leu Thr Arg Tyr Asn Tyr Gly
325 330 335

Gln Pro Pro Gly Thr Thr Thr Ala Gly Ala Val Gln Phe Lys Asn Gln
340 345 350

Val Ser Phe Asp Lys Asp Phe Asp Phe Asn Ile Arg Val Ala Asn Asn
355 360 365

Arg Gln Ser Asn Thr Thr Gly Ala Asp Gly Trp Gly Phe Met Phe Ser
370 375 380

Lys Lys Asp Gly Asp Asp Phe Leu Lys Asn Gly Gly Ile Leu Arg Glu
385 390 395 400

Lys Gly Thr Pro Ser Ala Ala Gly Phe Arg Ile Asp Thr Gly Tyr Tyr
405 410 415

Asn Asn Asp Pro Leu Asp Lys Ile Gln Lys Gln Ala Gly Gln Gly Tyr
420 425 430

Arg Gly Tyr Gly Thr Phe Val Lys Asn Asp Ser Gln Gly Asn Thr Ser
435 440 445

Lys Val Gly Ser Gly Thr Pro Ser Thr Asp Phe Leu Asn Tyr Ala Asp
450 455 460

Asn Thr Thr Asn Asp Leu Asp Gly Lys Phe His Gly Gln Lys Leu Asn
465 470 475 480

Asn Val Asn Leu Lys Tyr Asn Ala Ser Asn Gln Thr Phe Thr Ala Thr
485 490 495

Tyr Ala Gly Lys Thr Trp Thr Ala Thr Leu Ser Glu Leu Gly Leu Ser
500 505 510

Pro Thr Asp Ser Tyr Asn Phe Leu Val Thr Ser Ser Gln Tyr Gly Asn
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Gly Asn Ser Gly Thr Tyr Ala Ser Gly Val Met Arg Ala Asp Leu Asp
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Gly Ala
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<400> 22

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Ala Leu Ile Thr Gly Ala Ala Leu Leu Ala Arg Arg Arg Ser Lys Lys
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Glu Lys Glu Ser
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<210> 23
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Val Met Thr Leu Leu Val Gly Leu Gly Leu Met Lys Arg Lys Lys Lys
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Lys Asp Glu Asn Asp Gln Asp Asp Ser Gln Ala
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Tyr Ala Leu Leu Gly Met Leu Ala Leu Phe Ile Pro Lys Phe Arg Lys
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Glu Ser Lys
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Ala Phe Ala Thr Leu Ala Leu Leu Gly Ser Leu Ser Leu Leu Leu Phe
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Lys Arg Lys Glu Ser Lys
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Met Ala Leu Ile Ala Leu Ser Ser Ile Val Ala Phe Val Leu Pro Arg
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Lys Arg Lys Asn
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<400> 27

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1 5 10 15

Val Leu Leu Ala Gly Ile Gly Leu Ile Ala Thr Val Arg Arg Arg Lys
20 25 30

Ala Ser

<210> 28
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<213> Staphylococcus aureus

<400> 28

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1 5 10 15

Ser Ile Ile Gly Ile Ala Gly Leu Met Leu Leu Ala Arg Arg Arg Lys
20 25 30

Asn

<210> 29
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<212> PRT
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<400> 29

Leu Pro Lys Ala Gly Glu Thr Ile Lys Glu His Trp Leu Pro Ile Ser
1 5 10 15

Val Ile Val Gly Ala Met Gly Val Leu Met Ile Trp Leu Ser Arg Arg
20 25 30

Asn Lys Leu Lys Asn Lys Ala
35